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The Journal of Allergy

VOL. 9 SEPTEMBER, 1938 No. 6

Original Articles

THE SPECIFIC DIAGNOSIS AND TREATMENT OF POISON IVY (RHUS TOXICODENDRON) DERMATITIS*

A. H. W. CAULFEILD, M.B.
TORONTO, CANADA

IN A PREVIOUS publication[1] I reported the marked reduction in skin sensitivity as judged by quantitative patch testing of four individuals following a series of intramuscular injections of an extract of poison ivy. For this preparation I suggested the term "Rhus Tox. Oleo-antigen" contracted to the name of "Rholigen."† Each of the four subjects had invariably suffered severe—or, with certain of them, continuing attacks of dermatitis on the seasonal exposure occurring during their summer holidays. The injections and final patch testings were made before their re-exposure to the same environment during the summer of 1937. It would seem inappropriate if, in this communication, no reference were made to the practical results experienced by these four individuals during their re-exposure to the same environment.

These can be summarized briefly as follows:

CASE REPORTS

Case 1.—N. M., remained entirely free. Case 2.—F. H., noticed a few patches of discoloration which remained dry and were not itchy. He did not know if these were due to the poison ivy or not. Case 3.—N. J., suffered a dermatitis about one arm and shoulder; it remained localized and dry, disappearing in a week or so. It was discovered later by her father (a physician) that she had lain down on a piece of ground covered with poison ivy. Case 4.—McC. D., experienced much the same as Case 2, namely, scattered areas at different times that were discolored but remained dry and were not itchy. Cases 1, 3, and 4 were children, and no special precautions could be taken to avoid contact. Case 2 was a young adult who had for some years attempted to avoid actual contact as much as possible. Case 4, during an interview in my office in January, 1938, said he had repeatedly touched poison ivy leaves "to see what would happen."

*Presented at the Section of Medicine, Academy of Medicine, Toronto, Canada, February 8, 1938.

†The initial observations on the preparation of this type of extract are given in references 1 and 2; the effect of variations in the methods will be given in a later communication.

Following that publication a number of cases of dermatitis diagnosed as poison ivy were referred to me for treatment. These were first quantitatively patch tested. As my belief that the injections influenced materially the duration and severity of the dermatitis is based upon the effect of the injections on the duration and severity of the initial patch test, I will refer briefly to the tentative classification of this test as suggested in the previous report.[1]

The dilution of the oleo-antigen used for patch testing was one which had given a delayed mild reaction in two individuals who had regarded themselves as immune, but who had experienced relatively mild attacks after weeding the plant, one with and the other without gloves. This degree of reaction I termed "one plus." As more severe reactions, although also delayed, were experienced in other individuals known to have had attacks, the one plus was extended to moderate and severer forms. In all these delayed reactions vesiculation was absent and the spread limited to the area of the covering of cellophane, i.e., about 30 by 30 mm. The severer degrees of a one-plus reaction lasted for three weeks or longer. In general, the area itched for two to three weeks and soothing applications were necessary. The two- and three-plus reactions showed evidence of positiveness on removal, which consisted of an area of edema plus punctate papules. Both these degrees of reaction spread beyond the area noted on removal and vesiculation was marked, especially in the three-plus reactions. The four-plus reactions were indicated by both edema, papules, and red pin point dots on removal. The spread was greater and vesiculation more intense than in the three-plus reactions.

On further experience this tentative classification has been found to be fairly satisfactory, with certain modifications. So far in only one individual giving a one-plus delayed reaction has the spread gone beyond the area of cellophane covering, and in this instance slight vesiculation occurred. Also his past history with regard to the number of attacks to both poison ivy and many other types of excitants was unusual. Again the classification has been found inadequate with certain individuals tested after treatment. In this group a number have shown a superficial area of pigmentation on removal of the patch test. This area has not spread materially and has remained free from itching or infiltration. This slight or even questionable, but immediate, reaction has thus far been encountered only in those tested after treatment.

TREATMENT

The observations I wish to make under this heading can, I feel, be best presented if the order as given in the title is reversed and specific treatment dealt with before diagnosis.

Treatments by intramuscular injections have been given to 23 individuals begun either as a therapeutic measure during the presence of a

poison ivy dermatitis (in 14 cases) or prophylactically because of a past history of seasonal attacks (in 9 cases) confirmed by positive patch tests. In the majority of these latter the quantitative patch test was allowed to run its full course, except for the doubtful effect of topical applications.

In contrast with those dealt with prophylactically, intramuscular injections in those tested during an attack were begun usually as soon as the patch test showed a positive reaction, which was generally on removal. The earlier injections were given daily or more usually every second day if there was no reaction from the injection. Now, if it can be accepted as probable that a quantitative patch test would have the same severity and duration whether it was applied during an attack or during an interval of freedom, *then the difference in severity and duration of the patch test between these two groups affords definite proof that the injections were responsible for the rapid improvement in the actual clinical dermatitis itself.* As already stated, the duration of a patch test is three weeks or longer without treatment, whereas in those treated immediately the duration of the patch test was reduced to a few days (up to a maximum of about eight) and did not increase after the second or third injection. Coincident with this definite control of the anticipated increase in the patch test, there was an evident improvement of the clinical dermatitis itself.

Clinically, it has been my impression that poison ivy dermatitis is a self-limited disease, and for each individual depends upon the intensity of the exciting contact plus the susceptibility of the individual. Without the control which is afforded by the effect of treatment upon the patch test, it would seem to be difficult to estimate accurately the effect of the injections upon the attack itself in the majority of instances—largely because it is difficult to determine at what interval before spontaneous recovery would have manifested itself that treatment was started.

With these observations on the severity and duration of the patch test* without treatment in those treated prophylactically, two of the fourteen cases treated therapeutically during an attack are selected to support this contention.

CASE REPORTS

B., E. G. A., an adult, consulted me May 26, 1937. He stated he had been spending considerable time in the country recently, and about a week previously a dermatitis had begun on his hands and feet. This had increased in severity. At the time of consultation his hands were bandaged, and there were areas of dermatitis on the feet, ankles, and face. In several of the areas weeping vesiculation was very evident. Two years previously he had visited the same summer resort and had experienced two similar attacks. He had consulted a local physician and had

*The essentials of quantitative patch tests before and after treatment are (1) the method must enable one to apply exactly identical amounts, and (2) there should be no nonspecific reaction such as adhesive plaster might give. The method published[1] provides for both these considerations.

been told he had poison ivy dermatitis. (This vicinity I have since learned has poison ivy in profusion.) Patch tests were removed after twenty-four hours' application on May 27. The control was negative, whereas the poison ivy extract showed an area of edema, redness, and punctate dots, measuring 50 by 50 mm. This was estimated at a two- or, more likely, three-plus reaction. Injections were started with 0.5 c.c. of the poison ivy extract diluted 1:10,000 on May 27. On June 2, at which time the third injection of poison ivy extract was given, the patch test was reduced to 40 by 40 mm., and was dry. On June 5 the patient stated all irritation had stopped about June 2 in both the patch test and in the clinical areas of dermatitis. On June 12 he stated that on the previous week-end he found he had been standing in his bathing suit on a piece of ground covered by poison ivy but that afterward he had experienced no itching or dermatitis as a result. A total of ten injections were given ending July 7, with but one minor local reaction. After treatment, patch tests were made on July 15. When removed on the following day, there was nothing to see grossly; under a magnifying glass there were possibly one- or two-minute papules. By July 19 there was an ill-defined area of superficial discoloration, measuring approximately 7 by 7 mm., which was not itchy. On July 20 a fivefold increase of the extract showed, after twenty-four hours' application, an area of edema and papules measuring 10 by 15 mm. By July 22 this had increased to an area of 20 by 20 mm. without vesiculation, although it itched. On August 3 he reported that during the last week-end in the country he had purposely tramped through a patch of poison ivy in his bare feet and had remained free from any irritation. This trial afforded him positive proof of the effectiveness of his treatment.

B. B., aged 8 years, had suffered severe poison ivy dermatitis since he was 2 years old and during this time had spent only one summer out of Toronto—that was when he was 2 years old. A goodly part of the summer previous to consulting me was spent in attendance at the Hospital for Sick Children because of poison ivy dermatitis. His mother brought him to me on July 12, 1937, saying that this was his second attack that year. She could not give a date for the onset of the second attack as the first of several weeks' duration had not subsided before she realized he probably had started a second attack. On examination both hands were encased in cotton gloves, his arms were bandaged as was most of his face. Legs and body were so intensively involved that the only clear area which I could find to patch test was the anterior surface of the right thigh. On removal of the twenty-four-hour patch test on July 13 there was a dry red area with papules and edema, measuring 35 by 40 mm. This result I feel should not be classified, as this site reacts differently from the anterior surface of the forearm, but probably corresponds to a four plus had the usual site been used. The first intramuscular injection was given on July 13, namely, 0.12 c.c. poison ivy extract diluted 1:1,000. On July 19, when the third injection was given, the patch test was dry and reduced to 15 by 15 mm. No lotion had been used since July 15, at which time the gloves had been discarded. Injections were continued until August 5, at which time the entire attack had cleared. He was then taken to a camp—the second outing he had had in his lifetime. He returned on August 18 with two large vesicular patches on his hands. His brother who accompanied him contracted a severe attack of poison ivy dermatitis. The injections were continued, but on August 25 he "went to a fire" in his bare feet. Three days later the feet were "badly blistered" and he was confined to bed. The attack, however, remained confined to the feet and was of such short duration that he returned to the office for his injection on September 1. At this time he was about half way through the course of injections. These were continued on and off until January 24, 1938. The total number of injections was 26, the maximum number given to any one individual. Reactions of varying degrees followed nine of the injections; two of these were sufficiently severe local dermatitis to suggest postponement of his

injections temporarily, and three were moderately severe remote reactions. After treatment, patch test gave the following result: Twenty-four hours after removal on January 30, 1938, there was a questionable blush, measuring perhaps 6 by 6 mm., with one or two papules detectable with a magnifying glass; seventy-two hours later there was a dry dermatitis, about 10 by 10 mm., which was just palpable and was not itchy. The control area was negative.

Summary of the effect of treatment on the quantitative patch test done before and after completion of the course of injections is as follows. Twenty-three individuals with histories of attacks of poison ivy dermatitis, which were confirmed by patch tests, submitted themselves for treatment. Four stopped treatment before the full course was completed—the majority discontinuing as soon as the clinical attack subsided; 3 are continuing treatment; 16 have completed their course and have been quantitatively patch tested so that a comparison of both tests can be made.

The after treatment patch test in all the 16 individuals was reduced either to the lighter degrees of a one-plus reaction or was negative. In only four was itching present to a mild degree, in all the rest this feature was absent. Three of the 16 subjects were negative to the naked eye, but either a faint blush or a whitish papule could be detected with the magnifying glass in 2 of the 3. Thus, the degree of reduction was not equal in all. One case in particular (C. F. A., a physician) showed a relatively slight reduction. This case was unusual in many particulars. He stated he had had over 200 attacks, several of them extremely severe. He was 63 years of age and he knew he was sensitive to many other types of vegetation. The initial patch test done on July 28 was negative on removal. It became positive about forty-eight hours later, spreading to a maximum diameter of 30 by 30 mm., with slight vesiculation. The results did not lend themselves to the tentative classification I had adopted. At first I classified the result as a one-plus moderate, later changing it to two plus. In addition I found it difficult to raise the dose (because of reactions) for so mild a patch test result. Twenty injections were given before a satisfactorily high dose was obtained. The after treatment patch test was done on January 4, 1938. On removal after twenty-four hours it was negative. Later it became positive, was itchy, and on January 7 reached its maximum of 12 by 18 mm. Vesiculation was doubtful. Thus one might summarize by stating that, with one exception, the after treatment patch test was either negative (in the minority) or if positive could be classified as a mild or moderate form of a one-plus reaction. With this low degree of sensitivity very close contact, such as weeding, is seemingly necessary to induce a clinical attack.

Although all reactions were carefully measured and classified, in only three individuals were photographs obtained of the initial patch test. Two of these have completed their treatment (Figs. 1-5).

Fig. 1 shows a patch test after twenty-four hours' application, removed on July 10, 1937. An area of 15 by 15 mm. with edema and a few punctate dots appears. No treatment was given. Forty-eight hours later fine vesiculation was evident, measuring 20 by 20 mm., with surrounding area of edema 30 by 35 mm., and was classified as a two-plus reaction. After treatment, patch test removed after twenty-four hours'

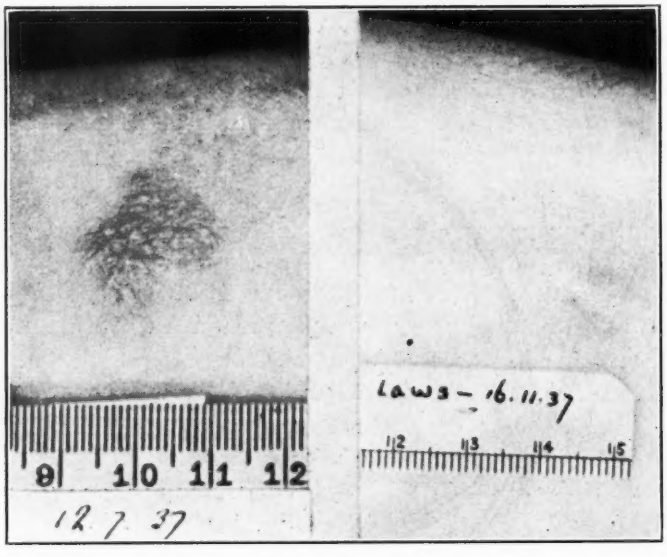

Fig. 1.—Quantitative patch tests. Before and after treatment. Appearance forty-eight hours after removal.

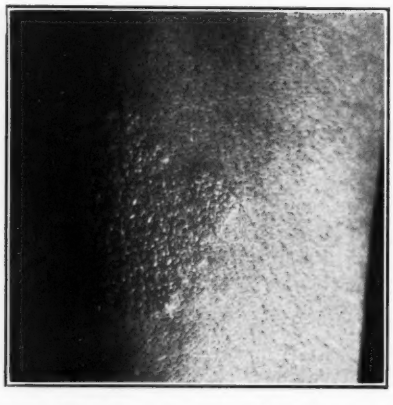

Fig. 2.—(Del. R.) Before treatment on removal.

application on November 14 was negative. Forty-eight hours later there was a barely detectable area of discoloration, about 5 by 10 mm., not palpable and not itchy. The number of injections given was 14.

Fig. 2 illustrates a patch test after twenty-four hours' application removed July 13. Edema with papular eruption measuring 35 by 35 mm. is seen. Seventy-two hours later, although a very small injection

had been given on July 14 (0.25 c.c. of dilution 1:10,000), vesiculation was intense and the entire area measured 60 by 70 mm. (Fig. 3). The reaction was classified as a three plus, possibly a four plus. The after treatment patch test removed after twenty-four hours on December 17, 1937, showed a barely detectable area of discoloration. The blue pencilled lines (Fig. 4) showed the control and the site of reaction. Seventy-two hours later this area measured about 10 by 10 mm., was barely palpable and was not itchy (Fig. 5). The after treatment results

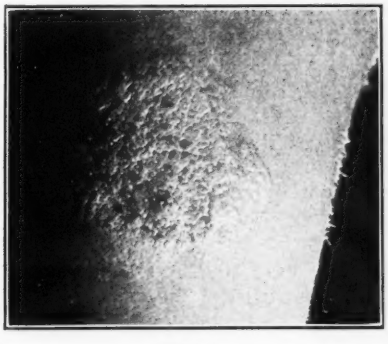

Fig. 3.

Fig. 4.

Fig. 3.—(Del. R.) Before treatment, seventy-two hours after removal.
Fig. 4.—(Del. R.) After treatment on removal.

Fig. 5.—(Del. R.) After treatment, seventy-two hours after removal.

illustrate the immediate reaction without material spread found only in after treatment tests. The number of injections given in this case was 18. These results are not the best obtained nor are they the poorest. I feel they represent, perhaps, a little better result than the average and, of course, could not have been selected ahead of time.

Dosage and Reactions.—These aspects are reciprocal; the greater the degree of sensitivity, the greater the number of injections which must be given if one is to avoid uncomfortable reactions. In other words, the increase in dose must be graded differently in different individuals.

The degree of sensitivity is, I believe, fairly accurately indicated by the quantitative patch test. But among a group giving the same degree of reaction there has been considerable difference in the rate of increase in dosage, which, of course, governs the number of injections necessary.

The least number of injections given has been eight. This individual, a physician, had experienced two attacks of poison ivy dermatitis on weeding the plant. Following treatment he was "patch negative" and subsequently weeded without an attack. Despite the fact that the increase in dose was each time relatively very large, no reactions were induced.

The largest number of injections so far has been 26 already cited in Case B. B. Reactions followed the injections as noted.

Character of Reactions.—The most frequently encountered has been a dermatitis about the site of the injection. This, probably, was on many occasions due to a leak back along the needle tract. That this is not always the case is proved by a dermatitis at some distance from the site of injection—such as scattered papules or an area of dry dermatitis, i.e., the remote reaction as described in the previous publication.[1]

SPECIFIC DIAGNOSIS

I approach this aspect of these remarks with considerable trepidation because of the fear that my experience with a relatively small number of cases will be misinterpreted from a statistical point of view.

At least 46 individuals have been patch tested with Rholigen—in a few instances with increasing strengths of the antigen if the initial test was negative. This number includes several who were either interested in seeing if they were susceptible to contact with poison ivy or who thought it likely that some attack of dermatitis previously experienced had been caused by poison ivy. In addition, the group includes a few cases in which patch testing was indicated but whose history was not at all suggestive that their dermatitis could possibly be regarded as due to poison ivy.

While the results with this small and rather heterogeneous group have been helpful to me personally, an analysis would be of doubtful value because of the different reservations incidental to this or that individual. From the total, however, a definite group can be separated on the simple basis of those which were patch tested with the standard dilution of Rholigen during an existing dermatitis and further subdivided into two categories as shown in Table I.

As shown in this table 25 cases were referred with the diagnosis already made of poison ivy dermatitis. For 4 other individuals no etiologic diagnosis had been suggested, but in whom for one reason or another different patch test substances including that from poison ivy had been used. Nine of the group of 25 gave either a two-, three-, or four-plus reaction, thus fully confirming the etiology. In 7 the patch

test was negative. Three of these had been admitted to either the Western Hospital* or St. Michael's Hospital.* With these 7 there would seem to be no doubt but that the dermatitis was not caused by poison ivy. In the remaining 9 cases a one-plus reaction was obtained. In 7 the attack was relatively mild and of short duration, so that the

TABLE I

RESULTS OF PATCH TESTING CASES OF DERMATITIS WITH RHOLIGEN

PREVIOUS ETIOLOGIC DIAGNOSIS	NO. OF CASES	2-, 3-, OR 4-PLUS REACTIONS	1-PLUS REACTION	NEGATIVE
Poison ivy	25	9	9*	7
None made	4	0	1†	3‡

*In 7 the dermatitis was mild in character and was most probably due to poison ivy.

†The dermatitis was not due to poison ivy and trial treatment had no effect.

‡Two of these were found to be instances of ragweed dermatitis.

clinical diagnosis would seem to be in accord with the results of the tests. The remaining 2 offer points of interest and I will briefly review their histories together with the one case in the group of 4 giving a one-plus reaction.

CASE REPORTS

C. G., aged 5 years, was seen on August 19, 1937. His mother said that a rash had appeared chiefly on his face about August 2 and was diagnosed by his physician as poison ivy. This plant was quite plentiful in the neighborhood. She said that last summer he had had an attack of poison ivy dermatitis. His dermatitis certainly did not suggest poison ivy to me, not only on account of its appearance but chiefly because at that time it was confined to his face. I suggested to his doctor that this was in fact not poison ivy even though he was slightly susceptible to the plant and would no doubt contract this condition if suitable contact with poison ivy were made. The diagnosis later was made of impetigo contagiosa.

H. W., aged 69 years, consulted me on September 29, 1937. He stated that during the war he was employed as a carpenter at Camp Borden (a concentration camp) and that there he with many others contracted poison ivy dermatitis. His attack, he said, was the worst of all and that despite hospitalization he had never been free since the initial onset. At the time he consulted me he had areas of dermatitis chiefly about the ankles and wrists, although there were a few areas elsewhere on the body and face. He was convinced that since the onset he had safely avoided all further contact with poison ivy. I explained that I did not see how a dermatitis could persist and be due to poison ivy. He was patch tested with a large number of other extracts to all of which negative results were obtained. But to the standard poison ivy oleo-antigen he gave a delayed one-plus moderate or severe reaction, measuring 25 by 25 mm., with edema and punctate papules. With no other indication available, treatment with poison ivy extract was begun on October 5. On October 12, when he had his third injection, he stated that there was no doubt that the dermatitis was better—it had "lost its sting and didn't irritate him." A week later the dermatitis had cleared up. After eleven injections of increasing strength, he was patch tested. The patch test was negative to the eye, though by the magnifying glass there was a doubtful blush over the area. He returned February 2 and

*I wish to thank Dr. Anglin and Dr. Broughton, respectively, for their kindness in carrying out the tests for me.

stated that recently his legs had begun to irritate him, especially at night. On examination there were scattered patches of erythema on the legs, especially about the thighs. The appearance was totally different from the deep seated infiltrative dermatitis present on his first appearance. One thinks of course of two possible explanations: first, that the original dermatitis was due to poison ivy, later becoming complicated by other factors, and secondly the possibility of a nonspecific effect from the injections.

In contrast to this astounding though unfinished clinical result, the abbreviated case history of the one instance of the group of 4 in Table I, giving a positive test is added.

C. G. O. consulted me on January 27, 1937, about a dermatitis which he stated had persisted since May, 1936. Patch tests with a number of materials were all negative, except to the standard extract of poison ivy. A series of 6 injections, rapidly increased in strength, had no effect, thus proving to me that his dermatitis could not be due to poison ivy.

Thus, in summary of this aspect with regard to specific diagnosis, the quantitative patch test affords, I believe, a clear-cut indication of the susceptibility of the individual with regard to contact with poison ivy. A positive result does not necessarily indicate that the etiology of an existing dermatitis is poison ivy. While the results of the test may be decisive, ordinary clinical judgment, in many instances, should be exercised.

SUMMARY

1. The extract from the poison ivy plant termed "Rholigen" suitably diluted for patch testing has been found of value in the differential diagnosis of dermatitis regarded as possibly due to contact with poison ivy.

2. Observations have been presented in support of the conclusion that the intramuscular injection of this extract in increasing amounts actively influences the severity and duration of an attack of poison ivy dermatitis.

3. Following an adequate series of intramuscular injections of this extract, all individuals susceptible to poison ivy dermatitis have shown a greatly reduced (with a questionable reservation in one case) or even a negative quantitative patch test.

4. Practical clinical results, based upon re-exposure to the same environment, have confirmed the theoretical conclusion that a satisfactorily reduced quantitative patch test coincides with clinical immunity to ordinary contact with this weed.

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ACTIVE IMMUNIZATION OF ALLERGIC INDIVIDUALS AGAINST TETANUS BY MEANS OF TETANUS TOXOID, ALUM PRECIPITATED REFINED*

HERMAN GOLD, M.D.
CHESTER, PA.

IT IS a well-known fact that the administration of horse serum is contraindicated in cases of horse dander sensitivity and is fraught with danger when attempted in other cases of allergy. Repeated injections are especially hazardous in the atopic individual. Hence, active immunization against tetanus, if feasible, should be of great practical value in the allergic group.

In March, 1937,[1] we reported our first attempts in this field. We now wish to present additional follow-up results:

From this and similar studies conducted on normal nonallergic individuals, we have found that the basic course of immunization should consist of two injections of 1.0 c.c. each of alum-precipitated toxoid, given about ninety days apart. Although patients respond well to the injection of 0.5 c.c. of the toxoid, we feel that 1.0 c.c. is an optimum dose.[2] The interval between the two injections may be as short as sixty days and as long as two years.[3]

In our entire experience, covering over 1,000 injections given in the last five years, we have encountered only one systemic reaction. This occurred in a nonatopic subject who developed hives one-half hour after the second injection of alum-precipitated toxoid. It is important, however, to remember that although refined, this antigen does contain traces of beef broth which may produce reactions in beef sensitive individuals. Slight to moderate reactions occur at the site of injection, but they subside in two to three days. They may be lessened by proper refinement of the antigen. In some individuals a nodule similar to that produced by diphtheria alum-precipitated toxoid may persist at the site of injection for several weeks.

The first dose of tetanus toxoid serves to prepare the host so that following a second injection there occurs a considerable increase in the antitoxin content of the blood. This state of "sensitization," produced by the first injection of toxoid, may last at least several years.[3] It is highly characteristic of artificial immunization. The natural occurrence of tetanus and recovery from this disease does not affect the antitoxin producing cells of the body in the same manner as the first dose of alum toxoid and cannot serve as its substitute. In other words, a subject that has recovered from tetanus still requires two doses of alum-

*Read before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 30, 1938.

TABLE I

TETANUS TOXOID, ALUM PRECIPITATED, REFINED No. 5961-1

Basic Course of Immunization: Two Doses

Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

CASE	CONTROL TITER	FIRST DOSE	DAYS AFTER FIRST DOSE TITER	DAYS BETWEEN INJECTIONS	SECOND DOSE	DAYS AFTER SECOND DOSE TITER												
						2	3	7	9	12	14	28-30	45	95-123	151-196	210-274	341-362	430-437
8096	0.003	0.5 c.c.	28 days	91	0.5 c.c.			-0.10			0.25			0.01			+0.01	
			0.003														-0.10	
9903	-0.003	0.5 c.c.	------	77	0.5 c.c.		-0.10	+0.25						0.10	+0.01		+0.01	
															-0.10		-0.10	
9912	+0.003	0.5 c.c.	30 days	90	0.5 c.c.	-0.10			+0.25					+0.01		+0.01	+0.01	
	-0.01		-0.003											-0.10		-0.10	-0.10	
9914	+0.003	0.5 c.c.	37 days	93	0.5 c.c.			-0.10				+0.01	0.01	0.01		0.01		
	-0.01		0.003									-0.10						
9915	+0.003	0.5 c.c.	31 days	87	0.5 c.c.		-0.10	-0.10			+0.25			+0.01	0.01		+0.01	
	-0.01		0.003											-0.10			-0.10	
9921	+0.003	0.5 c.c.	27 days	84	0.5 c.c.			+0.25						+0.003			+0.01	
	-0.01		-0.003											-0.01			-0.10	
9916	+0.003	0.5 c.c.	49 days	84	0.5 c.c.			+0.10				+0.25		0.01	0.003		+0.01	
	-0.01		-0.003					-0.25									-0.10	
9920	+0.003	0.5 c.c.*	28 days	91	0.5 c.c.*			+0.10			+0.25			0.10	+0.01		+0.01	
	-0.01		-0.003												-0.10		-0.10	
8099	0.01	1.0 c.c.*	28 days	91	1.0 c.c.*			+0.25			+0.25			0.10		+0.01	+0.01	
			0.25					-0.50			-0.50					-0.10	-0.10	
9906*	-0.003	1.0 c.c.	31 days	87	1.0 c.c.		-0.10	-0.10			+0.25			0.50	+0.10		0.10	
			0.003												-0.25			
9910	-0.003	1.0 c.c.	44 days	87	1.0 c.c.	-0.10				-0.10		0.25		0.01	+0.003		+0.01	
			-0.003												-0.01		-0.10	
8094	-0.003	0.5 c.c.*	199 days	199	0.5 c.c.			+1.0			+0.25	+0.25		+0.25	+0.01	+0.01		+0.01
			-0.01					-5.0				-2.0			-0.10	-0.10		-0.10
10000	-0.003	0.5 c.c.*	123 days	206	0.5 c.c.			-0.10			+1.0	+0.25		0.10	+0.003	0.003		+0.01
			-0.003									-2.0			-0.01			-0.10

\+ more than − less than *76812-1

precipitated toxoid before a suitable amount of tetanus antitoxin can be demonstrated in his blood.

The rate of both production and elimination of tetanus antitoxin following completion of the basic course of immunization varies a great deal in different individuals. This variability appears to be an individual function independent of sex, age, and color, and is just as pronounced in the allergic as it is in the nonallergic individual. In view of this variability, several questions must be answered before active immunization can be recommended as a routine procedure. First, what is the actual amount of antitoxin necessary to give protection against tetanus infection? From our published studies on passive immunization and from an analysis of the available data on the experimental production of tetanus in actively immunized animals, we feel that 0.1 unit of antitoxin per cubic centimeter of blood serum is necessary to insure protection against this disease. Although there is some suggestive experimental evidence that tetanus antitoxin per se may not be the only factor responsible for immunity and although smaller amounts than 0.1 unit of antitoxin may be sufficient in many cases, we believe that at the present time it is safest to insist on the presence of 0.1 unit of antitoxin as a minimum necessary for protection. Otherwise, a false sense of security may result. Second, how soon after the basic course of immunization is completed, does the protective value of 0.1 unit develop?

Table I will throw some light on this question as well as on the duration of the immunity. Thirteen patients were immunized against tetanus while undergoing treatment for pollinosis. The antigen used, lot No. 5969, was prepared by the Sharp and Dohme Laboratories from a toxin containing over 20,000 M.L.D. Antigenic tests performed with this alum-precipitated toxoid showed that the injection of 0.5 c.c. into standard guinea pigs produced at the end of six weeks 5.0 units of tetanus antitoxin per cubic centimeter of blood serum. A similar titer was produced by the injection of 1.0 c.c. of the toxoid.

Following completion of the basic course of immunization it was found that 5 of 11 subjects tested on the seventh day, still showed less than 0.1 unit. At the end of two weeks all patients but one showed more than the minimum protective value of 0.1 unit. The exception is the only refractory case we have encountered thus far. This patient, however, developed a good protective titer following a third injection of toxoid. When tested again three to four months after injection of the second dose of toxoid, 6 subjects, or 50 per cent, of the group had dropped below 0.1 unit. Four additional members of this series showed –0.1 unit when retested three months later. Another subject dropped below the 0.1 unit level nine months after the second injection. Only one individual showed 0.1 unit one year after immunization.

These findings point out the need of insuring protection by passive immunization with 1,500 units of tetanus antitoxin if an injury occurs

TABLE II

TETANUS TOXOID, ALUM PRECIPITATED, REFINED NO. 11623-1

Antitoxin Response to a "Repeat" or Third Dose (1.0 c.c.)

Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

CASE	INTERVAL BETWEEN SECOND AND THIRD DOSES	TITER BEFORE THIRD DOSE	DAYS AFTER THIRD DOSE TITER													
			2	3	4	5	6	7	8	10	27-30	35-38	105	133	181	217
9903*	348 days	+0.01		+0.01		1.0		+5.0				1.0	+0.5			+0.25
		-0.10		-0.10				-7.5					-1.0			-0.50
9912*	349 days	+0.01			+0.01			0.50				+3.0	+1.0			1.0
		-0.10			-0.10							-5.0	-3.0			
9915*	348 days	+0.01		+0.01		0.25		3.0				2.0	+0.25			+0.50
		-0.10		-0.10									-0.50			-1.0
9921*	344 days	+0.01		+0.01		+2.0		15.0				+5.0	+0.25			0.25
		-0.10		-0.10		-3.5						-7.5	-0.50			
9920*	341 days	+0.01			+0.01	+1.0		10.0		+10.0		+3.0	+1.0			+0.50
		-0.10			-0.10	-2.0				-15.0		-5.0	-3.0			-1.0
8096*	341 days	+0.01			+0.01	+0.10		0.50				+0.50		+0.25		+0.10
		-0.10			-0.10	-0.25						-1.0		-0.50		-0.25
9914*	255 days	0.01		+0.01		0.10		+2.0								
				-0.10				-3.5								
9916*	362 days	+0.01			+0.01			+1.0							+0.10	
		-0.10			-0.10			-2.0							-0.50	
8094*	430 days	+0.01		0.10		+0.5			+5.0			2.0				
		-0.10				-1.0			-10.0							
10000*	437 days	+0.01			+0.01		2.0					+0.50				
		-0.10			-0.10							-1.0				
8099†	361 days	+0.01					+1.0			+ 3.0	2.0		1.0			0.50
		-0.10					-3.0			- 5.0						
9910†	352 days	+0.01	+0.01						+1.0		1.0			+0.01		+0.01
		-0.10	-0.10						-3.0					-0.10		-0.10
9906†	346 days	0.10			+0.10			+3.0				10.0	+3.0			+1.0
					+0.25			-5.0					-5.0			-3.0

*Basic course of immunization: two 0.50 c.c. doses.

†Basic course of immunization: two 1.0 c.c. doses.

+ more than

- less than

during the interval that elapses between the injection of the two doses of toxoid and for a week or two following the second dose, when active protection has not as yet fully developed. They also bring out the variable and rather rapid loss of antitoxin that occurs during the first few months following active immunization. Because of this it has been deemed advisable to inject a third or "repeat" dose of toxoid at the time of injury in order to bring up the antitoxin content of the blood to a protective level. In this regard it is important to determine the rapidity with which the antitoxin titer is restored to a protective level following the "repeat" injection.

Our group of 13 subjects received such a "repeat" injection of 1.0 c.c. of toxoid one year after the basic course of immunization had been completed, when their antitoxin titer had dropped to less than 0.1 unit. The antigen used, lot No. 11623-1, when injected into standard guinea pigs in doses of 0.5 and 1.0 c.c., respectively, produced at the end of six weeks a little more than 3.0 units of antitoxin per cubic centimeter of pooled serum.

Table II shows the response elicited by the "repeat" injection. During the first four days, only one of 10 subjects that were tested showed 0.1 unit. The rest had –0.10 unit. On the fifth day, all those tested showed values of 0.1 unit or more. Some actually had more than 1 or 2 units of antitoxin per cubic centimeter of serum, a very marked increase in titer. On the seventh day, one subject showed 15.0 units while the rest had values well above the minimum titer required for protection. Between the first and fourth or fifth weeks following the "repeat" injection, 8 subjects showed a rather decided drop in titer and 3 patients showed an increase. After the first month, they all showed a loss in the antitoxin content of their blood. When the group was retested three to four months after the "repeat" injection, one subject showed a drop to +0.01 –0.10 unit. A second patient showed +0.10 –0.50 unit, when retested three months later. Six members of the group that were available for testing two hundred seventeen days after the "repeat" dose still showed a good protective titer, with an average of about 0.5 unit per cubic centimeter of blood serum.

The thirteenth member of the group, Case 9906, had a control titer of 0.10 unit. Within a month the antitoxin content of her blood increased to 10 units, and two hundred seventeen days after the stimulating dose, this subject still showed +1.0 –3.0 units per cubic centimeter of blood serum. This study would indicate that a third dose of alum toxoid, given at the time of injury, will restore the antitoxin titer of the blood of an individual previously immunized against tetanus, to a protective level of 0.1 unit or more within four to five days after the injection. It is stated[4] that the incubation period of tetanus in man is usually from six to fourteen days, and is directly proportional to the amount of toxin and the severity of the disease. With a short period of incuba-

tion, six days or less, the disease is almost invariably fatal. Whether this acute type of tetanus can be prevented by the "repeat" injection of toxoid is open to further investigation.

Although the present series is small, the follow-up antitoxin titrations performed after the "repeat" injection seem to indicate a more lasting retention of a protective titer of 0.1 unit or more than was the case after the basic course of immunization (2 injections of alum-precipitated toxoid). This is perhaps due, in part at least, to the high antitoxin titer produced by the "repeat" injection. The loss in antitoxin is not, however, directly proportional to the amount previously present in the blood, but appears to vary in different individuals regardless of this level.

CONCLUSIONS

1. Allergic subjects can be immunized safely against tetanus by means of two injections of 1.0 c.c. each of alum-precipitated toxoid given ninety days apart.

2. The response of allergic subjects to such a basic course of immunization is the same as that elicited in nonallergic individuals.

3. If an injury occurs during the interval of time that elapses between the injection of the two doses of toxoid and for a week or two following the second dose, one must resort to the prophylactic injection of 1,500 units of tetanus antitoxin for protection against tetanus.

4. The antitoxic protection that develops in allergic subjects following the basic course of immunization is variable in duration as in nonallergic individuals. This necessitates the injection of a third or "repeat" dose of alum-precipitated toxoid (1.0 c.c.) upon the occurrence of an injury. This will bring the antitoxin content of the blood up to a protective level. One-tenth of a unit or more of tetanus antitoxin can be demonstrated in the blood in four to five days following the "repeat" injection of toxoid.

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314 E. BROAD STREET

THE TOTAL, FREE, AND ESTER CHOLESTEROL CONTENT OF THE SERUM IN HAY FEVER AND IN ASTHMA*

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IN CONTRAST to the numerous investigations on the concentration of cholesterol in the serum in inflammatory and degenerative diseases, few extensive studies have been carried out on the content of this lipid in the blood in allergic diseases, particularly hay fever and asthma. About ten years ago, Fornet, Benö, and Dzsinich[1] reported that a hypercholesterolemia occurred during every attack in patients with asthma. They stated, moreover, that the asthmatic attacks in such patients could be aborted by the intramuscular injection of cholesterol. Bray[2] credits Cantonnet for originally demonstrating this hypercholesterolemia in 6 patients with asthma. In a study of 40 allergic children, Payne and Bray[3] found that in the interval in which their subjects were free from asthma, the blood cholesterol varied from 111 to 232 mg. per cent, the normal cholesterol in children ranging from 100 to 200 mg. per cent. Bullen and Bloor[4] studied 14 patients having seasonal or perennial types of hay fever or asthma, or both. Their subjects manifested an average total cholesterol of 152 mg. per cent, while their 12 normal controls showed an average of 162 mg. per cent. These writers also observed no definite difference in the degree of saturation of the plasma fatty acids between adults suffering from asthma and hay fever and those who did not have these diseases.

In other allergic states, e.g., migraine, the blood cholesterol was found to be elevated. Rémond and Rouzaud[5] found an average value of 210 mg. per cent in 46 patients suffering from migraine; Mochlig[6] observed the average blood cholesterol to be 225 mg. per cent in 27 patients with this disease. On the other hand, Hansen[7] has shown that the eczema in infants, presumably also an allergic manifestation, is accompanied by a low serum cholesterol.

MATERIAL AND METHODS

In the present study the cholesterol partition of the serum was studied in 121 adult patients with hay fever or asthma, at a time when they were free from attacks. These were divided into four groups, namely, (a) hay fever under treatment (49 cases), (b) asthma under treatment (50 cases), (c) hay fever before institution of treatment (11 cases), and (d) asthma before institution of treatment (11 cases). The findings in

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the first two groups, embracing 99 cases, are reported; the latter two groups have been omitted from the statistical analyses because of the small number of cases studied. Reference will be made to these later.

The subjects studied were typical cases of bronchial asthma and seasonal hay fever under treatment and selected from those attending the Allergy Clinic of the New York Post-Graduate Hospital. The duration of the allergic complaint ranged from one month to nine years. The sera were obtained, in all instances, at a time when the individuals were free from attacks, and, in the case of the hay fever patients, weeks before the onset of their seasonal paroxysms. While the blood specimens were procured during a course of weekly scheduled treatments, they were always obtained by venepuncture before the injections were given at the afternoon session of the clinic. In all instances, the hay fever patients were of the Fall type and were sensitive clinically and by test to ragweed pollen. Their weekly treatments consisted of injections of ragweed pollen extract. In 17 of the 49 cases, sensitiveness to the rare grasses also was present and considered in treatment.

Of the 50 cases of bronchial asthma, 30 were of the simple skin sensitive type with positive cutaneous reactions to the various inhalants or foods. These often manifested associated allergic complaints but without complicating upper respiratory infections. In 20 cases, the asthma was entirely infective in origin or of the mixed type, both positive skin reactions and upper respiratory infections being present.

The cholesterol partition in the serum was carried out by the method of Schoenheimer and Sperry,[8] using the modification for the colorimeter developed by Fitz[9] in this laboratory. Our findings have been compared statistically to the values obtained by Sperry[10] (who used the same method but without the colorimeter modification) on 126 specimens of blood from 91 normal adults.

RESULTS

In order to conserve space, the protocol of the individual results has been omitted. In Table I the findings have been compared statistically with the values obtained by Sperry in normal subjects. The standard deviation and probable error of the mean of the total cholesterol observed by Sperry have been calculated from his data and are included in this table. It will be observed that in the treated hay fever group, the sex distribution was 31 males and 18 females, with an age range of 16 to 60 years. The average total cholesterol for this group was 222 ± 67 mg. per 100 c.c. of serum as compared to the values observed by Sperry in normal adults of 210 ± 50 mg. The average per cent of free cholesterol in total cholesterol was 34 ± 8.3 mg. per cent, which is somewhat higher than the average normal values. Sperry observed the per cent of free cholesterol in total cholesterol to vary from 24 to 30 per cent, with an average of 27 per cent in normal adults. Of the 49 treated hay fever

cases, the per cent of free cholesterol in total cholesterol was below 24 per cent in 4 subjects and above 30 per cent in 29.

In the treated asthma group, the average total cholesterol was 199 ± 50 mg. per cent; the average per cent of free cholesterol in total cholesterol was 32.4 ± 7.5 mg. per cent. Here again, the per cent of free in total cholesterol was somewhat higher than the normal values. Of the

TABLE I

STATISTICAL ANALYSIS OF THE TOTAL, ESTER, AND FREE CHOLESTEROL IN NORMAL SUBJECTS (SPERRY) AND IN PATIENTS WITH HAY FEVER AND WITH ASTHMA

			NORMAL SUBJECTS (SPERRY)	TREATED HAY FEVER CASES	TREATED ASTHMA CASES
No. of cases			126	49	50
Sex	Male			31	24
	Female			18	26
Age range (years)			19-43	16-60	15-71
Serum Chol. Range	Total Chol.	Min.	131	89	113
		Max.	392	330	322
	Free Chol.	Min.		38	37
		Max.		145	99
	Ester Chol.	Min.		51	61
		Max.		296	260
	Total/Free	Min.	24	20	16
		Max.	30	55	49
Total Chol.	Arithmetic Mean		210	222	199
	Standard Deviation*		±49.5	±66.7	±50.0
	Probable error of mean†		2.98	6.43	4.77
	$\frac{d}{\sigma D}$ ‡			1.14	1.32
Ester Chol.	Arithmetic Mean			148.8	136.6
	Standard Deviation			±56.2	±44.7
Free Chol.	Arithmetic Mean			73.1	62.3
	Standard Deviation			±21.2	±13.9
Total Free	Arithmetic Mean		26.9	34.0	32.4
	Standard Deviation		±1.4	±8.3	±7.5

*Standard deviation $\sigma = \sqrt{\frac{\Sigma\ (d^2)}{N}}$

Where $\Sigma\ (d^2)$ represents the summation of the squares of the individual deviation from the mean, and N the number of determinations.

†Probable error of mean $= 0.6745\ \frac{\sigma}{\sqrt{N}}$

Where σ represents the standard deviation, and N the number of determinations.

‡$\frac{d}{\sigma D}$ represents the difference between two means divided by the standard error of the difference.

The standard error of the difference σD is calculated from the formula

$$\sigma D = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$$

Where σ_1 and σ_2 represent the standard deviations of the two groups, and N_1 and N_2 represent the number of determinations in the two groups.

50 cases of treated asthma reported in this paper, 6 were below 24 per cent and 27 were above 30 per cent.

In the 22 patients with untreated hay fever and asthma (11 in each group), the average total cholesterol was 198 and 197 mg. per cent, and

the average free cholesterol in total cholesterol was 29 and 31 per cent, respectively. The degree of variation from the treated allergic groups is not noteworthy. As mentioned above, the small number of untreated cases studied did not permit statistical analysis.

Although the average total cholesterol in the treated hay fever group is greater than the average normal figure, and in the treated asthma group somewhat lower, the variation from normal is not striking in either group. Moreover, the difference between the means of the normal and hay fever group on the one hand, and the normal and asthma group on the other, each divided by the standard error of the difference of these means give values of 1.14 and 1.32, respectively. These figures lack significance from a statistical standpoint.

SUMMARY

Although there is a tendency for the total blood cholesterol to be slightly elevated above the average normal in patients with treated hay fever and slightly below normal in patients with treated asthma, the results lack significance from a statistical standpoint. In both groups, however, the per cent of free cholesterol in total cholesterol is definitely elevated above the average normal. The results in a smaller series of patients with hay fever and asthma before the institution of treatment were not unlike those observed for the treated groups.

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TOBACCO ALLERGY AND THROMBOANGIITIS OBLITERANS*†

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THE problem of tobacco allergy as a cause of thromboangiitis obliterans has been the subject of several controversial reports. Harkavy[1] and his associates concluded from their studies that these cases are allergic in most instances and are sensitive to tobacco. Sulzberger,[2] in another study, lent support to Harkavy's work. Since then further studies have been reported by Chobot,[3] Trasoff,[4] and Maddock and his colleague,[5] which are contradictory to those of Harkavy, Silbert, and Sulzberger.

ETIOLOGY

The exact etiology of thromboangiitis obliterans is not known. Practically all of the workers in the field have noted the clinical relationship between the development of the disease and the use of tobacco. Silbert[6] has stated that in over 1,000 consecutive cases he has not seen one in a nonsmoker, and a similar experience has been reported in recent years from most of the leading vascular clinics. Prior to 1930, cases were reported in nonsmokers, but since this subject has received more careful study, such reports have practically disappeared from the literature. In addition it has been consistently observed that the lesions do not heal well, indeed often not at all, while the patient continues to smoke. Furthermore, lesions recur quickly in many patients if smoking is resumed even many months after healing. On the other hand, the lesion does not tend to progress unless the patient is smoking. This experience has been confirmed in the Vascular Clinic of the New York Post-Graduate Hospital.

The vasoconstricting effects of smoking on the peripheral vessels of the extremities have been conclusively demonstrated by thermocouple reading and capillary microscopy by the studies of Maddock and Coller,[5, 7] Barker,[8] Wright and Moffat,[9, 10] Johnson,[11] and Merle and Multhaupt,[12] and by plethysmographic studies by Lampson.[13] While these studies may explain why smoking is definitely aggravating in any condition when the circulation is already markedly impaired, they do not prove that it is the original causative factor.

Friedlander, Lasky, and Silbert[14] found that by injecting rats intraperitoneally with 60 per cent denicotinized tobacco they could produce

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gangrene in 33 of 48 male rats, but none of the 12 female rats developed the lesion.

These various observations appear to establish a definite relationship between the use of tobacco and thromboangiitis obliterans. The problem as to whether this is an allergic phenomenon or not is the subject of the present paper and will be discussed in detail.

Mention should be made of the more important various other approaches used in attempting to determine the etiology. Sex seems to play some part in the picture since thromboangiitis obliterans occurs in the female so rarely. McGrath[15] has reported that he could protect female rats but not male rats from gangrene produced by ergot, which is similar to thromboangiitis obliterans, by the injection of theelin. Ergot has long been recognized as the cause of a type of gangrene which is pathologically similar to thromboangiitis obliterans. The clinical course of ergotism is apt to be more rapid and it usually occurs in certain areas of the world where large amounts of rye flour are grown and consumed. Ergotism may also occur following the use of ergot-containing medications. Many patients with thromboangiitis obliterans, however, have not been exposed to this factor.

Trauma must be accepted to be an aggravating factor but no satisfactory evidence has been advanced to prove that it constitutes a true primary cause.

Race was formerly considered to be important since it was considered to be practically confined to Hebrews, but it has been since observed in large numbers in most of the racial groups and probably will be demonstrated in all as further studies are made.

Age is apparently important since practically all cases first occur between the ages of 18 and 50 years, but we do not understand the factors responsible for this. It is possible that instead of the female having endocrine secretions of a protective nature, the answer lies in the fact that the male during his actively potent years possesses a secretion which renders him susceptible to this condition and that with the onset of the male climacteric this substance is no longer formed, thus preventing the onset of the disease in later life.

Infection remains one of the most likely of the etiologic possibilities. The apparently inflammatory appearance of the lesions of thromboangiitis obliterans has led to recurrent studies by many workers in an endeavor to find a bacterial cause for the disease. While organisms which were not considered to be contaminants have repeatedly been reported, none have been established to be causative agents thus far. Perhaps the most interesting observation in this regard is the report of Allen and Lauderdale[16] of a case of accidental transmission of thromboangiitis obliterans from a patient to the operating surgeon as a result of the piercing of the palmar flesh by a spicule of bone from an in-

volved toe. So far as we can ascertain this is the only such instance on record. We have been unable to duplicate this condition by the transplantation of involved bone into cats or rabbits. Syphilis has been eliminated by the rare association of the two conditions, it being no more than the average coincidental statistical rate.

Goodman[17] has for some years been attempting to establish the relationship of old typhus infections to thromboangiitis obliterans on the basis of case histories and skin testing by using suspensions of Rickettsia prowazeki, but this theory cannot be accepted without confirmation of his work which seems unlikely in the light of our present knowledge of the racial and geographic distribution of the two diseases. The history of exposure to typhus fever is practically unheard of in our thromboangiitis obliterans patients. A few of the older patients who migrated from the Near East have been exposed to typhus, but the younger generation born in this country have not had that exposure.

Many other theories of possible etiology have been advanced, but on the basis of present knowledge none are worthy of mention in this brief paper.

The question as to what effect, if any, peripheral vascular diseases have on the development of skin reactions is of importance in evaluation of the results reported here and elsewhere. Lewis[18] found that only in instances where marked venous stasis or complete arterial occlusion was present would histamine fail to form a wheal. Furstenberg and Gay[19] confirmed these observations. In these same experiments they discovered that circulatory obstruction aided tissue sensitization in performing passive transfer tests.

In the present study, nonallergic cases of generalized arteriosclerosis with cardiac decompensation and lower extremity edema were included. Numerous distinct marked wheals were obtained to tests with tobacco and control extracts. The upper extremities were used for testing and adequate circulation was present for the formation of wheals in those cases where true sensitivity to the testing extracts existed.

Nowhere in the clinical picture of thromboangiitis obliterans are found features characteristic of any of the known or proved allergic conditions, i.e., asthma and hay fever.

It is important in interpreting any statistics which involve such a variable as "skin reactions" to have a common basis for such readings. The standards of interpretation as proposed by Cooke[20] in 1915 and which are recognized by practically all allergists and workers in the field of immunology as the normals for allergic diseases have been used here.*

*Original wheal = 0.2 to 0.3 cm.
Slight reaction = 0.5 to 1 cm. (negative and slight reactions have been called negative).
Moderate reaction = 1 to 2 cm. (moderate or marked reactions are positive).
Marked reactions = 2 plus cm.

TABLE

THROMBOANGIITIS

CASE NO.	AGE	SEX	DURATION OF SYMPTOMS IN YEARS	PHYSICAL FINDING					SKIN TESTS TO TOBACCO & CONTROL SOL.	USE OF TOBACCO
				RUBOR	PALLOR	PHLEBITIS	ULCER	GANGRENE		
1	34	M	3	++	++	++	Yes	0	Negative	Moderate
2	47	M	2	0	++	0	No	0	Negative	Moderate
3	32	M		++	++	0	No	0	Negative	Moderate
4	44	M	1/3	++	++	0	No	0	Negative	Marked
5	29	M	2/3	+++	+++	0	No	0	Negative	Moderate
6	59	M	15	++	++	0	Yes	0	Moderate	Slight
7	43	M	1/6	++	++	++	No	0	Negative	Moderate
8	42	M	7	++	++	++	No	0	Negative	Marked
9	32	M	6	+++	+++	0	Yes	Yes	Marked	Marked
10	43	M	2	++	++	0	No	0	Negative	Marked
11	30	M	1/12	++	++	0	Yes	0	Negative	Moderate
12	46	M	1½	++	++	0	No	0	Marked	Marked
13	50	M	6	+++	+++	+	Yes	Yes	Negative	Marked
14	39	M	4	++	++	0	No	0	Negative	Marked
15	47	F	3	++	++	0	Yes	0	Marked	Marked
16	44	M	1	++	++	0	Yes	Yes	Moderate	Marked
17	40	M	1	++	++	0	No	0	Marked	Marked
18	41	M	6	+++	+++	0	No	0	Negative	Moderate
19	27	M	2½	+++	+++	0	Yes	Yes	Negative	Moderate
20	33	M	½	++	++	0	No	0	Moderate	Moderate
21	38	M	1/6	+	+	0	Yes	0	Negative	Marked
22	42	M	1	+++	+++	0	Yes	0	Moderate	Moderate
23	39	M	1	+	+	0	Yes	0	Moderate	Marked
24	40	M	¼	+	+	0	No	0	Negative	Moderate
25	23	M	½	+	++	0	Yes	0	Moderate	Moderate
26	40	M	1/12	++	++	0	Yes	0	Negative	Moderate
27	33	M	1 1/6	++	++	0	No	0	Negative	Moderate
28	22	M	2	++	++	0	No	0	Moderate	Moderate
29	33	M	1½	++	++	0	Yes	Yes	Negative	Moderate
30	34	M	5	++	++	+	Yes	Yes	Negative	Marked
31	40	M	1/12	+++	+++	+	Yes	Yes	Negative	Marked
32	39	M	15	++	++	0	Yes	Yes	Moderate	Marked
33	43	M	1/6	+	+	0	No	0	Moderate	Marked
34	40	M	1	++	++	++	Yes	Yes	Marked	Marked
35	45	M	6	++	++	0	No	0	Moderate	Slight

I

OBLITERANS

FAMILY OR PERSONAL ALLERGY	OSCILLOMETRIC READINGS BELOW ANKLE		CLAUDICATION TIME	X-RAY	TREATMENT	PROGRESS
	RT.	LT.				
No	0	1/8	1½ Blocks	No sclerosis	Mecholyl and Typhoid injections	Developed ulcer of 4th left toe before healing—50% Improvement to date
No	½	½	4 Blocks	0	Mecholyl tissue extract	Can walk 10-12 blocks
No	0	0	1 Block	0	Mecholyl and typhoid injections	Slow improvement
No	0	½	½ Block	0	Typhoid injections	Unknown
No	0	0	Rest pain	No sclerosis	Typhoid injections	Moderate improvement
No	1/6	1/6	Rest pain	0	Heat and Bergers exercises	Unknown
No	½	0	3 Blocks	Osteoarthritis	Pavex	Stationary
Yes	2	5	Rest pain	Negative	Mecholyl	No change
No	1/8	1/8	Rest pain	0	Amputation and typhoid	Improved
Yes	1	1/8	2 Blocks	0	Tissue extract	Improved
No	0	0	1 Block	Negative	Typhoid injections	Improved
Yes	¼	1/8	5 Blocks	Negative	Mecholyl and typhoid	Improved to 15 blocks
No	0	0	Rest pain	Negative	Amputation and typhoid	Improved some
No	0	0	Rest pain	0	Typhoid injections	Improved—ulcers healed
No	0	0	1 Block	Negative	Typhoid injections	Improved
Yes	0	0	Rest pain	Negative	Typhoid injections	Good
Yes	0	0	5 Blocks	Negative	None	Unknown
No	0	0	5-10 Blocks	0	Typhoid injections	Improved
No	0	1	Rest pain	Negative	Amputation and typhoid	Improving
No	+	+	5 Blocks	0	Typhoid injections	Symptom free
No	1/8	0	1 Block	0	Typhoid injections	Improved
No	0	0	Rest pain	Negative	Typhoid injections	Improved
No	1/8	0	1 Block	Negative	Typhoid injections	Improved
No	1/8	1/8	2 Blocks	0	Typhoid injections	Improved
No	0	1	4 Blocks	0	Typhoid injections	Improved
No	1/8	¼	2 Blocks	0	Mecholyl and typhoid injections	Improved
No	0	¼	Cold weather	0	Typhoid injections	Improved to 10 blocks
No	0	½	Rest pain	0	Typhoid injections	Improved
No	0	0	Rest pain	Negative	Amputation and typhoid	Improved
No	0	0	Rest pain	0	Typhoid injections	Improved
No	2	¼	Rest pain	Sl. sclerosis	Amputation and typhoid	Improved slightly
No	0	0	Rest pain	0	Typhoid injections	Same
No	0	0	5 Blocks	0	Typhoid injections	Improved slightly
No	0	1	Rest pain	No sclerosis	Amputation and typhoid	Improved slightly
No	¼	1/16	5 Blocks	0	Typhoid injections	Improved

From a study of previous reports, the problem of tobacco allergy in thromboangiitis obliterans seems to resolve about the question of skin tests as an index of positive allergy.

Experience in testing allergic subjects reveals a small percentage of patients who skin test negative but have clinical allergy, i.e., hay fever, asthma, or rhinitis. Many of these patients, after removal of the ex-

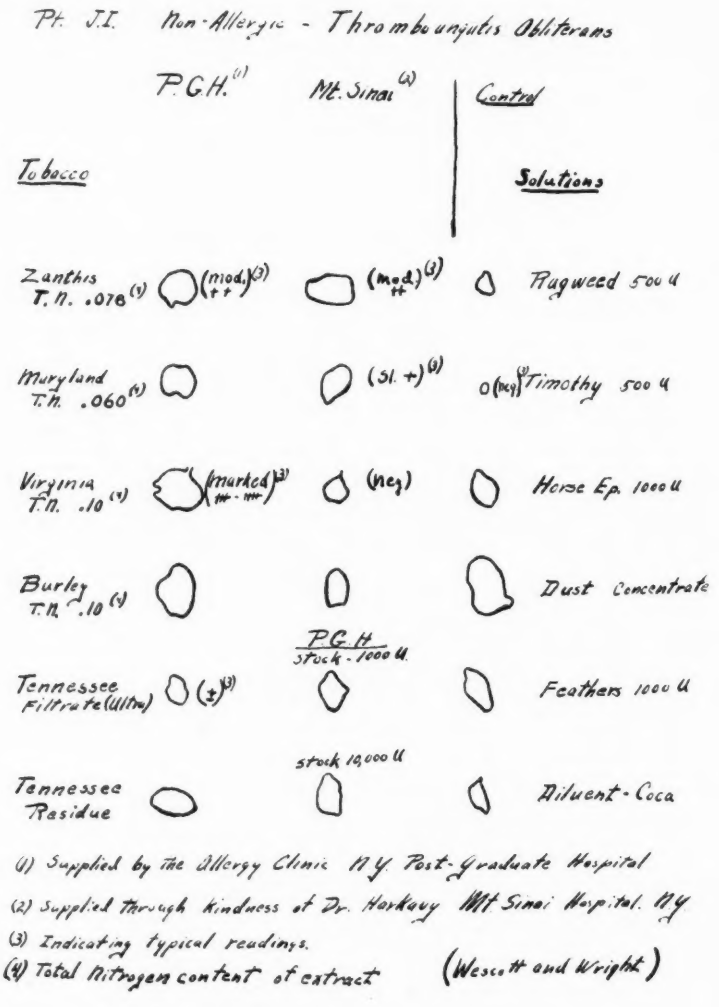

Chart 1.—Tracings of skin reactions (11/1936).

citant or by other specific treatment, get better. The reverse is also true, that many truly allergic subjects give positive skin reactions to substances to which they are clinically insensitive. This nonspecificity of skin tests is even of greater importance in testing for sensitivity in diseases which are not considered strictly allergic in nature.

TABLE II

CONTROLS

CASE NO.	AGE	SEX	DIAGNOSIS	PHYSICAL FINDINGS	TOBACCO TESTS	USE OF TOBACCO	ALLERGY	
							PERSONAL	FAMILY
1	45	M	Arteriosclerosis	Peripheral vascular impairment	Moderate	++	Yes	Yes
2	28	F	Vasomotor rhinitis	None	Negative	+	0	0
3	50	M	Polycythemia vera	Peripheral vascular obstruction with polycythemia	Negative	+++	0	?
4	23	M	Vasomotor instability	Cold extremities with cutis mamurata	Marked	++	0	0
5	60	M	Arteriosclerotic occlusion	Peripheral vascular impairment	Negative	+++	0	0
6	46	F	Raynaud's syndrome	Cold extremities	Moderate	0	0	Yes
7	47	M	Arteriosclerosis	Peripheral vascular impairment	Negative	++	0	0
8	39	F	Raynaud's syndrome	Obesity cold extremities	Marked	0	0	0
9	30	M	Normal	Normal	Negative	0	0	0
10	28	M	Normal	Normal	Negative	++	0	0
11	25	M	Migraine	Normal	Moderate	0	Yes	0
12	59	M	Arteriosclerosis	Peripheral vascular impairment	Negative	++	0	0
13	36	M	Varicose ulcers	Venous obstruction in extremities	Moderate	++	0	Yes
14	47	M	Arteriosclerosis	Peripheral vascular impairment	Marked	++	0	0
15	59	M	Arteriosclerosis	Peripheral vascular impairment	Moderate	+++	0	0
16	54	F	Diabetes mellitus	Peripheral vascular impairment	Moderate	0	0	0
17	50	F	Varicose veins	Venous circulatory disturbance	Negative	++	0	0
18	58	M	Coronary sclerosis	Hypertension	Marked	+++	0	0
19	61	M	Arteriosclerosis; diabetes mellitus	Peripheral vascular impairment	Moderate	++	0	0
20	40	M	Arthritis	Peripheral vascular symptoms	Moderate	+++	Yes	0
21	31	M	Cardiac degeneration	Cardiac impairment	Moderate	+	Yes	Yes
22	52	M	Coronary thrombosis	Cardiac impairment	Negative	++	0	0
23	50	M	Pneumonia	Cardiac impairment	Negative	0	0	0
24	45	M	Gonococcal arthritis	Peripheral vascular impairment	Negative	0	0	0
25	45	M	Coronary occlusion	Obesity; cardiac decompensation	Marked	+++	0	0
26	55	M	Angina pectoris	Underweight; moderate arteriosclerosis	Moderate	+++	0	0
27	50	M	Arteriosclerosis	Moderate arteriosclerosis	Slight	+	0	0
28	59	M	Arteriosclerosis	Moderate sclerosis	Moderate	++	0	0
29	37	M	Normal	Normal	Slight	0	0	0
30	40	F	Asthma	Overweight; asthma	Marked	0	Yes	Yes
31	24	F	Raynaud's syndrome	Peripheral vascular disease	Negative	0	0	0
32	22	M	Asthma	Normal	Slight +	++	Yes	Yes
33	20	F	Neurodermatitis	Obesity	Negative	0	Yes	Yes
34	40	M	Normal	Normal	Slight	+	0	0
35	34	M	Arthritis	Arthritis	Negative	++	0	0

The present study* consists of a detailed analysis of 35 cases of thromboangiitis obliterans, with an equal number of control cases made up of miscellaneous subjects with arteriosclerosis, varicose veins, Raynaud's syndrome, and normal patients. The cases of thromboangiitis obliterans were carefully selected and determined to be typical of this disease. Atypical or doubtful cases were not used in this study. Tables I and II show the essential features of each case.

It is interesting to compare these results with those of the other authors whose differences are best demonstrated by Table III.

TABLE III

RESULTS OF SKIN TESTS OF TOBACCO IN NORMALS AND PATIENTS WITH THROMBOANGIITIS OBLITERANS

AUTHOR	PERCENTAGE POSITIVE REACTIONS			
	THROMBOANGIITIS OBLITERANS		CONTROLS	
	No.	*Per Cent Reacting Positive*	*No.*	*Per Cent Reacting Positive*
Harkavy and Romanoff	69	69 Per cent tobacco only 9 Per cent other allergens also 78 Per cent total	200 Smokers	11 Per cent tobacco only 27 Per cent other allergens also 38 Per cent total
Sulzberger	13	78 Per cent tobacco only 15 Per cent other allergens also 93 Per cent total	Smokers 95	36 Per cent
			Nonsmokers 58	16 Per cent
Trasoff, Blumstein, and Marks	31	16 Per cent	Normal nonsmokers 52	21 Per cent
			Normal smokers 40	47 Per cent
			Allergic smokers 17	47 Per cent (34 Per cent)
			Allergic nonsmokers 24	25 Per cent (34 Per cent)
Chobot	0		Asthmatic children 53	52.9 Per cent
Westcott and Wright	35	42.8 Per cent total (tobacco only 5 per cent)	35	48 Per cent (Tobacco only 8 per cent)
	Smokers 35	42.8 Per cent	35 Smokers 24	50 Per cent
	Nonsmokers 0	0	35 Nonsmokers 11	36 Per cent
	Allergic* 5	60 Per cent	35 Allergic* 9	67 Per cent
	Nonallergic 30	40 Per cent	35 Nonallergic 26	39 Per cent

*Family or personal history.

Our results are rather in agreement with those reported by Trasoff and his co-workers. The discrepancies seen in comparison to the figures of Harkavy and Romanoff almost disappear when their reactions are interpreted according to the standard reading of skin reactions in the

*The extracts used were in part supplied through the kindness of Dr. Harkavy and in part from the Allergy Clinic of Dr. Will Cook Spain, New York Post-Graduate Hospital.

cases of thromboangiitis obliterans, although some discrepancy remains in the control group.

One of the methods of verifying true skin sensitivity is by the method of passive transfer. We realize that skin testing is not without its sources of error, and in order to minimize these sources we performed these passive transfer experiments on nonallergic nonsmokers. We used serum from patients giving good marked reactions to tobacco and tried each serum on two recipients. In eight experiments we observed one fairly positive result. This is rather conclusive proof that tobacco antibodies are very inactive or are absent in even those 42.8 per cent of thromboangiitis obliterans subjects who do give positive skin tests for tobacco. A recent report by Chobot[21] emphasizes the limited value of passive transfer as a diagnostic criterion. He found numerous positive transfers in the absence of any recognized allergic disease. Tobacco

TABLE IV

SKIN TESTS FOR TOBACCO SENSITIVITY

Statistics on Basis of Interpretation Which Includes Slight and Slightly Moderate Reactions as Positive

HARKAVY				WESTCOTT AND WRIGHT			
THROMBOANGIITIS OBLITERANS		CONTROLS		THROMBOANGIITIS OBLITERANS		CONTROLS	
No.	*Positives*	*No.*	*Positives*	*No.*	*Positives*	*No.*	*Positives*
69	78 Per cent (54)	200	38 Per cent (76)	35	71 Per cent (25)	35	74 Per cent (26)

Same Series Analyzed on Basis of Standard Methods of Interpretation Disregarding Slight and Slightly Moderate Reactions

HARKAVY				WESTCOTT AND WRIGHT			
THROMBOANGIITIS OBLITERANS		CONTROLS		THROMBOANGIITIS OBLITERANS		CONTROLS	
No.	*Positives*	*No.*	*Positives*	*No.*	*Positives*	*No.*	*Positives*
69	43 Per cent (30)	200	19 Per cent (38)	35	42.8 Per cent (15)	35	48 Per cent (17)

Note: Compared on this basis the apparent discrepancy disappears in the thromboangiitis obliterans series but remains in the control series.

sensitivity as determined by skin tests was found in 48 per cent of our control series as compared to 42.8 per cent in the thromboangiitis obliterans group. This may be because 27 per cent of the controls were potential or true allergic subjects as compared to 14 per cent in the former group. It happened that 86 per cent of these allergic subjects showed moderate to marked reactions in both groups when tested with tobacco and control solutions.

The work raises the question as to whether or not these interpretations by many authors as positive allergic reactions are not really nonspecific irritations carrying no significance whatsoever as regards the presence of a truly hypersensitive state. It is well known that many varieties of testing may have this nonspecific effect to a more or less degree; the extracts of house dust, pyrethrum, wool, and among the foods, rice, frequently produce this misleading effect, which can be proved to be nonspecific through clinical test.

SUMMARY

1. A study of the problem of specific hypersensitiveness of the skin to tobacco in 35 typical cases of thromboangiitis obliterans and 35 controls was made.

2. The patients with thromboangiitis obliterans did not show a higher evidence of positive skin reactions than the control group.

3. The high incidence of positive skin reactions to tobacco tests reported by other investigators and interpreted as allergic reactions is considered due to some of the many nonspecific reactions from chemical irritation.

4. Thromboangiitis obliterans is not caused by an allergic type of tobacco hypersensitiveness.

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THE EMOTIONAL COMPONENT OF BRONCHIAL ASTHMA*†

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THE clinical study of the allergic diseases has brought about a better differentiation of seemingly similar conditions and has evolved a therapeusis based on immunologic principles. It is but natural, therefore, that in the past the discussions before this Association have dealt mainly with the immunologic, the diagnostic, and the therapeutic data relative to these diseases. Now that these are assuming a more constant form and allergy is emerging from its tempestuous youth, I believe the time has come to study the emotional component of those with allergic disease and no longer confine ourselves to the impersonal processes involved in the concept of allergy.

Because of the lawlessly variable circumstances under which bronchial asthma occurred, and undoubtedly abetted by the 80 per cent cures reported by diverse therapies, it was inevitable that the term "neurosis" became a part of its definition. The trend of medical thought is illustrated by following its definition through twelve editions of a standard textbook. In the first edition of Osler's "Principles and Practice of Medicine" (1892) bronchial asthma is defined as "a neurotic affliction, characterized by hyperemia and turgescence of the mucosa of the smaller bronchi and a peculiar exudate of mucine. The attack may be due to direct irritation of the bronchial mucosa or may be induced reflexly by irritation of the nasal mucosa and indirectly, too, by reflex irritation from the stomach, intestines, or genital organs." Bronchial asthma remained a primary neurotic affliction through eight editions of this textbook. In the ninth edition (1920), the definition was altered to read "bronchial asthma is a reaction of an anaphylactic nature in sensitized persons and in others, a reflex neurosis." Not until the twelfth edition, in 1935, was the word "neurosis" omitted from the definition. Under the caption, etiology, however, there is the subhead "psychical causes," which states: "In some patients an anxiety neurosis or emotional disturbance plays some part and not infrequently this is an important factor in producing an attack in one who has had asthma." I believe that this is the consensus of physicians in the United States at the present time, just as the belief that it was a primary neurotic affliction, was the accepted one in 1892. This period of forty-three years represents the period of transition from neurosis as the cause of all bronchial

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asthma to a psychic influence in some cases, and was brought about by the study of anaphylaxis and the conception of allergy. Our present knowledge of clinical allergy allows us to begin a restudy of bronchial asthma and its relation to the emotions.

The respiratory process is one of the most deep lying and fundamental of vital functions. In the history of the human species, the word "breath" is closely bound up with ideas relating to life, spirit, and soul. Beginning with the Bible where it states, "And the Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life; and man became a living soul,"[1] which has its contemporary analogue that to be alive, legally, the lungs of an infant must give evidence of having drawn a breath, and concluding with the generally accepted assumption that when death overtakes us, we return to that state from which the breath of life enlivened us, mankind has had ever before him the indispensability of this function for his existence. Emotions affect the respiratory function in everybody but without unusual connotation when unassociated with morbific influences. The catching of the breath in grief or fear, the sighing of sadness, the rapid breathing of excitement and anticipation, the expansion of the chest in joy, the choking of anxiety are so frequently observed, that in literature they became the symbols for such emotions. But, any morbid process interfering with its easy and unrestrained performance will be regarded with either apprehension, or fear, or terror, or even panic. As in every other disease, a psychologic element is present and the realization of the inherited significance of respiration makes for a better understanding of the individual with bronchial asthma.

The emotional influences begin early in life and the reaction of children to discomfort or disease depends in a great measure, if not wholly, upon the attitude of those in their environment. Unstable parents will likely have unstable children and, as Clarkson[2] emphasizes, the potentially allergic child is born with both a psychic and somatic handicap. Dependent to a large extent upon the medical and psychologic guidance, such a child becomes either an egocentric, overly receptive adult with a predisposition to react to all types of stimuli, or a healthy adult, or if some discomforts remain, one with a philosophic outlook upon his travail.

There has been a great deal of experimental work, mostly pneumographic, on the relation of the psyche to the respiratory function. It has been reported that attention decreased the inspiratory expiratory quotient;[3] that there is a distinct respiratory curve during the process of seeing, recognizing, and naming an object;[4] that truth and falsehood have distinct respiratory symptoms;[5] that pleasure, pain, anger, disgust, wonder, fear, laughter, and hatred produce changes in the depth or amplitude of respiration;[6] that under hypnosis, the respiratory activity can be influenced by suggestion;[7] and that hypnosis can induce, as well

as inhibit, episodes of bronchial asthma in the latter instance, even when exposed to the substance giving a positive cutaneous reaction.[12]

The influence of hypnosis upon cutaneous reactions has also been studied. Wittkower[8] made the following observations: (1) A patient specially suitable for these purposes was, under hypnosis, given the suggestion that the scent of roses is specially harmful to her. It was easy to produce the conditioned reflex so that, even in a waking state, the slightest smell of roses, even the belief that roses were in the vicinity, was sufficient to produce asthmatic attacks. A cutaneous test with rose extract, performed after several weeks' training, was negative. (2) A demonstrable cutaneous allergy cannot be removed by suggestion. By analogy with the well-known investigations concerning the production of skin blisters, hemorrhages, and necroses by suggestion, an attempt was made to inhibit the development of the blister after intradermal injection of allergens. In two specially suitable patients a change of the local reaction could not be observed. Diehl and Heinicken[9] were able to increase or decrease the size of the cutaneous reaction by suggestion in three patients under hypnotic influence. They do not state whether an attempt was made to cause the disappearance of the skin test by the same method, but Clarkson[2] reports the following: "On preliminary investigation an asthmatic girl, aged 18, gave a severe cutaneous reaction to an intradermal test for egg sensitization. A wheal one inch in diameter surrounded by a raised erythematous zone three and a half inches across, developed around the site of inoculation. Next day the test was repeated whilst the patient was deeply hypnotized. The suggestion was given that no reaction would occur. The patient was kept under hypnosis for half an hour and the suggestion was frequently repeated. No wheal developed, and there was no erythematous blush. Next day the experiment was repeated in the patient's normal state, and the original wheal was obtained." Even in this respect, where one might expect unequivocal results, there are diametrically opposed observations. From the clinical standpoint, because the psychogenesis of bronchial asthma is a very old concept, the literature is replete with studies asseverating this concept. But even the later literature, when reviewed in the light of the present knowledge of clinical allergy, more logical reasons appear for the cure or betterment of these patients than the stressed psychic factors. It seems that those interested in allergy pay too little attention to the psyche and that those interested in the psychic conditioning of bronchial asthma are not aware of the possible allergic explanations for the vagaries of this disease.

Given a case of bronchial asthma, how many of the ups and downs depend on the emotions? As illustrations I will give the following experiences: A 34-year-old married woman with annual asthma and occasional attacks during the winter, skin sensitive to pollen, inhalants other than pollen, and foods, has been under observation since 1928. The at-

tacks of bronchial asthma are characterized by tremendous re-enforcement of the voluntary muscles of expiration and an unusual degree of fear. During a period when she had had no asthma for some time, I was asked to stop at the home to determine whether a liquid medicine she just had refilled by the pharmacist was all right. She thought that the pharmacist had made an error in compounding the prescription because it looked and smelled differently. She had not tasted it. I looked, smelled, and tasted it; agreed that it was not that which she had been taking, and took it with me to show the pharmacist. She had neither subjective nor objective bronchospasm. About thirty minutes later the patient learned that what I had tasted was hair tonic. She feared that it was poisonous and had asthma over a period of four hours, requiring a total dose of 3 c.c. of adrenalin, hypodermatically, for its control.

From the psychoanalytic viewpoint this patient had an ideal background to explain her emotional responses. She was the only child of an overly solicitous and overly protective, but domineering mother, with whom the patient and her husband lived. Every detail in this household, including the purse strings, was under the suzerainty of this matriarch, and neither the social status nor the age of the patient allowed activities which excluded the mother. The medical history of the patient was given by the mother and all past illnesses were described with the superlative adjective. Since becoming the medical advisor of this family group, every complaint of any member was viewed by the mother with great alarm and a forerunner of imminent calamity. This environment was conducive to bringing about the excessive fear and the thought that her asthma was the worst possible event that could befall one, and explains the extreme voluntary expiratory efforts during the bronchospastic episodes as the means of escape from an impending catastrophe.

Because under observation fear was followed by bronchospasm, one wonders how often and to what degree this emotion influenced other bronchospastic episodes in this patient, and to what degree and how often it is an influence in others.

A lad of 3 years with bronchial asthma, skin sensitive to pollen and inhalants other than pollen, had been habituated to sleeping with his mother. The asthma was satisfactorily controlled by therapy based on the cutaneous reactions. When the mother stopped sleeping with him (without asthma he no longer needed his mother's aid and comfort), the nocturnal attacks recurred and were controlled this time by habituating him to sleeping alone.

A similar instance in different guise is that of an 11-year-old boy with perennial vasomotor rhinitis and annual bronchial asthma, which lately was extending further into the winter, existent over a period of six years. He was a typically spoiled child of oversolicitous and overanxious parents. He refused to take medicine in any form, would not eat or drink during his periods of discomfort, and when well ate only bread, cake,

potato, meat, and candy. By therapy based on cutaneous reactions, aided by appropriate psychotherapy, it was possible to control the perennial vasomotor rhinitis and the severer attacks of bronchial asthma. He persisted, however, in having periods of bronchial asthma in the morning which prevented his getting to school by nine o'clock. Perhaps it was only a coincidence, but these attacks ceased when arrangements were made with the school authorities to admit him any time during the morning.

These cases are the extremes of one's experiences and exemplify the concept of a reaction pattern which can be activated by many kinds of stimuli along facilitated pathways. However, the explanation may be simpler. It is commonplace for dyspnea to induce wheezing in the individual with bronchial asthma. May not the dyspnea per se attendant upon the emotion of fear in the first patient and the dyspnea of the cantankerous child in the second and third instances be the cause of the wheezing without calling upon a complicated theory for an explanation?

A 54-year-old married woman was first under observation during 1931 for a period of five months. The history was that of vasomotor rhinitis and nocturnal cough which sometimes brought on mild wheezing, but not to the degree of needing adrenalin. The cutaneous tests were negative. The clinical impression was that of paranasal sinus infection. Her complaints were always out of proportion to the objective signs. She was susceptible to suggestion, but demanded immediate favorable results from each suggested plan. There was a large element of fear which probably was the basis for her impatience and irritableness during her periods of bilateral nasal blockage and for her refusal of hospitalization. She left my care and returned five years later. Some of my colleagues had greater persuasive powers than I, for during that period she had had all her teeth removed and bilateral Caldwell-Luc operations. Unfortunately she now had what she termed asthma, for which she had been taking 10 c.c. of adrenalin, hypodermatically, daily in 1 c.c. doses for several years, in addition to her original complaint of alternating nasal blockage and discharge. To her pre-existing fear, impatience and irritability, there was now added hyperkineticism and manual tremor, a pulse rate of 130 per minute and a blood pressure of 170/110 (in 1931 it was 120/80), and a great increase in the number of agents which she thought caused her symptoms. This time assent to hospitalization was given readily, where it was determined that the adrenalin was taken for the sense or feeling of oppression in the chest rather than for undoubted bronchospasm. "I took it to prevent a hard attack" was the admission finally obtained. It was easy to prove to her that smaller doses of adrenalin relieved as satisfactorily as the ones she had been taking, so that finally, relief followed 0.05 c.c., but it was difficult to reduce the number of doses a day. By dint of persuasion, however, she eventually needed none. Simultaneously, it was neces-

sary to disabuse her mind of the erroneous notions of the causation of her asthma. The consultant in rhinology advised no further therapeutic measures. Skin tests were negative. Definite severe bronchospasm followed the ingestion of acetyl salicyclic acid and of phenobarbital, which postponed her improvement and which in retrospect may account for some of the severe bronchospasm in past years, and the fear of these accounted for her frequent use of adrenalin. Up to the present time she has periods as long as three months without adrenalin and is convinced that the oppression in her chest is associated only with infection; moreover, that 0.05 c.c. adrenalin is sufficient to relieve it and that she should take no phenyl-containing drugs. Discordant domestic relationships added their psychic retardment to our therapeusis.

In our experience there are similar instances wherein the failure of dramatic or painful therapeutic procedures, or of unsupervised self-medication have led to persisting disablement. While it may be rightfully said that such instances are iatrogenic rather than psychogenic, nevertheless, it is the emotional adjustment of the individual to his discomfort brought about chiefly by allaying fear which aids in their eventual improvement.

It is not necessarily true that bronchospasm will vanish immediately when the offending allergen is avoided. When bronchospasm occurs frequently, it becomes a conditioned reflex, and the bronchi retain this reaction as tenaciously as they previously maintained a normal function, so that a full rectum, or a distended stomach, or a turgescent turbinate, or an emotional stimulus may become a trigger mechanism which provokes a spasm through the vegetative nervous system, not only during the period of absorption of an allergen but also for some time after such an allergen is avoided. The clinical evidence at the present time is that these stimuli will induce bronchospasm only in allergic individuals.

Fear and apprehension attend all human illness or discomfort so that, because of the inherited significance of breathing, one can assume with justice that these emotions may have a greater influence on the course of bronchial asthma than the other emotional factors recorded in the literature.[8, 10] Psychotherapy, mostly as persuasion and suggestion, will help, not in the sense that it removes the cause, but rather as part of a re-educational program. The allurement of the allergen should not cause us to forget the patient, for the therapeutic plan depends upon what kind of a patient has the disease.

The physician should always be aware of the emotional potentialities of his patient and particularly of the destructive effect of disappointment. In many, overemphasis of the importance of mechanical diagnostic procedures with their implication of mechanical accuracy causes further emotional imbalance and unnecessary as well as unjust criticism of the medical profession when the results are not up to the expectations of the patient. Further harm is done by promising too much from

therapeutic procedures, especially those that are painful, and finally, in many, unsupervised self-medication brings about chronicity and invalidism more often than bouncing health.

In summary, if the asthma is unassociated with personality problems, one should treat it as such, having due thought of the probability of inducing unfavorable emotional influences by inept emphasis upon diagnostic procedures and by unconsidered insistence upon therapeutic measures of indeterminate outcome. If the asthma is associated with emotional instability, one must treat the patient with all his problems as well as the local complaint.

I will conclude with the following quotation:[11] "There are moments, of course, in cases of serious illness when you will think solely of the disease and its treatment, but when the corner is turned and the immediate crisis is passed you must give your attention to the patient. Disease in man is never the same as disease in the experimental animal, for in man the disease at once affects and is affected by what we call the emotional life. Thus the physician who attempts to take care of a patient while he neglects this factor is as unscientific as the investigator who neglects to control all the conditions that may affect his experiment."

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INTRAPULMONARY INHALATION OF BENZEDRINE*

Preliminary Report of Some Clinical Effects

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TO SPARE asthmatic patients the necessity of hypodermic injections for the relief of attacks, Rowe and Graeser[1] substituted, with much success, the inhalation of nebulized adrenalin chloride in 1:100 solution. Subsequently, Barach[2] reported comparable effects from neosynephrin vapor in one case. In both methods the apparatus is too cumbersome to be carried and used by the patient in his daily activities. Because the sympathomimetic benzedrine base (benzyl-methyl-carbinamine) is volatile, cheap, stable, pharmacologically similar to adrenalin and especially effective on topical application in the nose, it occurred to us that its peroral intrapulmonary inhalation might be preferable and equally effective.

This is a preliminary presentation of our experience with the effects of peroral benzedrine inhalation. It is hoped that it will stimulate more general studies of the principles involved and that the uses and limitations of this symptomatic remedy will be more quickly established than if the report were withheld for more detailed study. The present observations concern themselves with (1) the effects of intrapulmonary benzedrine inhalation on the vital capacities of six normal subjects, (2) the visible bronchoscopic effects of the inhalations on three normal and on three swollen bronchial mucosae, and (3) the symptomatic relief afforded 17 asthmatic patients.

A commercial benzedrine inhaler was discarded early because the supplementary volatile oils were invariably disagreeable. As a substitute surgical gauze was loosely packed into two inches of one end of a six inch glass tube, 1 cm. in diameter. It was slightly indented in the center to prevent aspiration of the gauze which was then saturated with 0.5 c.c. of pure benzedrine base. When not in use, the ends were covered with rubber caps to prevent evaporation.

Patients were instructed to exhale completely, hold the breath, close the nose with the fingers of one hand, insert the tube almost to the uvula with the other hand, and close the lips firmly around the tube. They were then told to inhale as deeply as possible. This procedure was repeated at arbitrary intervals of from forty to sixty seconds for from

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The benzedrine base used in this experiment was supplied through the courtesy of Smith, Kline, and French Laboratories, Philadelphia, Pa.

six to ten inhalations in the vital capacity experiments with normal subjects and also in the asthmatic patients. In the bronchoscopic experiments the inhaler was applied to the operator's end of the bronchoscope for six inhalations at thirty-second intervals.

In the vital capacity experiments, six normal young subjects used the spirometer until their individual vital capacities were approximately the same on several successive measurements. Then they inhaled the benzedrine ten times at one-minute intervals. Three minutes after the tenth inhalation, the average of three additional vital capacities was taken. There were increases in these normal individuals of 2, 5.7, 9, 24, 5.3, and 15 per cent, respectively.

In the bronchoscopic inhalation experiments, the bronchial mucosae in three subjects were entirely normal as far as could be seen. After four inhalations, the mucosa of each had blanched appreciably. After six inhalations, the blanching was even more definite. In three patients their markedly swollen and reddened bronchial mucosae became considerably paler and less swollen after the fourth inhalation. After the sixth, the lumen of the main bronchus in two instances was increased

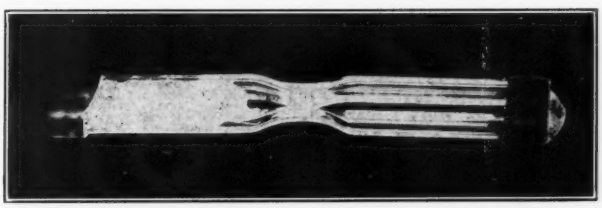

Fig. 1.

in diameter by an estimated 10 per cent, thus aiding materially in the bronchoscopic examination.

The following is a description of the typical response to benzedrine inhalation in 12 of 17 patients with asthma of varying degree. During the first three inhalations, the patient described feeling the drug down to about the level of the second or third rib anteriorly. With the third or fourth inhalation, the effect was felt at about the level of the fourth or fifth rib. With each subsequent inhalation the drug was felt somewhat lower, until by the sixth to eighth, the sensation was referred to the upper abdomen. By the fourth or fifth inhalation, the sense of constriction or air hunger was lessened, and by the sixth to eighth inhalation, it was significantly or entirely relieved.

In 12 of the 17 cases there was significant and grateful relief from the discomfort of the asthma. The total number of attacks relieved was about sixty. Of these, 25 were mild, and 35 were moderately severe attacks. In five other patients nine attacks were not relieved. This makes a total of 69 attacks in which benzedrine inhalation was used. In eight of the relieved cases, the cough resulting from the inhalation

was negligible. In four, the cough was troublesome until sputum was raised. In five relieved cases, the sputum raised after the inhalation was negligible. In seven, more than half an ounce was raised. The usual number of inhalations required for relief was six. The variation in the number of inhalations required in these 12 cases was four to ten. In two relieved cases, asthma was aggravated transiently the first one or two times it was used. Adrenalin, minims three, was given with more marked relief within five minutes than adrenalin alone had produced in larger doses during a period of over a week. Subsequent attacks were relieved by inhalation alone. In two relieved cases also aggravated by

TABLE I

BENZEDRINE INHALATION

RESULTS IN 17 CASES

Number cases relieved		12
Number attacks relieved		60
Mild		25
Moderately severe		35
Number cases not relieved		5
Number attacks not relieved		9
Associated cough		
Negligible		8 cases
Troublesome		4 cases
Associated sputum		
Negligible		5 cases
Over ½ ounce		7 cases
Usual number inhalations		6
Variations		4-10
Number relieved attacks needing adrenalin after inhalations		2
Number relieved cases needing ephedrine and amytal after inhalations		2
Number attacks aggravated by inhalations		2
Number attacks completely relieved by auscultatory signs		2 in 69
Side effects in 69 attacks		
Bad taste	Once	
Sleeplessness	Twice	
Burned throat	Twice	
"Unpleasant"	Once	
Excessive unproductive cough	Once	
Comparable to adrenalin inhalation		2 cases
Adrenalin plus inhalation better than either alone		5 cases

inhalation temporarily, ephedrine and amytal capsules were taken with greater and prompter relief than had been obtained in more than a week by ephedrine and amytal capsules alone in frequent doses. Inhalation alone relieved subsequent attacks in these two patients. The effect of inhalations on auscultatory signs was considered in about fifteen attacks. In two, the auscultatory signs of asthma completely disappeared. These signs were abundant before the inhalations. In the sixty-nine attacks the following side effects were noted: a disagreeable taste, once; sleeplessness, twice; burning throat and lungs, twice; "unpleasant," once; excessive unproductive cough, once; aggravation of the

asthma requiring repeated doses of adrenalin, twice. Two patients who had used adrenalin 1:100 inhalation previously stated that the effect of the benzedrine inhalation was entirely comparable, subjectively, to the adrenalin inhalation. In five patients the combination of three minims of adrenalin, plus the inhalation of benzedrine, was accompanied by greater subjective relief than from either remedy alone.

There seem to be two syndromes of simple relief from the inhalations. In those in whom the cough was negligible after inhalation, there seemed to be a direct and uncomplicated increase in the ability of the patient to breathe comfortably. In the others, the inhalations seemed to loosen exudate from the bronchi with resultant cough and expectoration. While they were coughing and expectorating, the symptoms were apt to be slightly worse. When approximately one-half ounce to an ounce of sputum had been raised, the patients were usually quite comfortable. In several instances mentioned above, adrenalin or ephedrine was necessary to complete the relief in the first one or two attacks in which inhalation was used. In several instances the auscultatory phenomena of asthma were somewhat more pronounced after the inhalation in spite of greater subjective relief. While not listed in Table I, the maximum number of attacks for which the benzedrine was inhaled by patients under close observation was about five in twenty-four hours. In four patients, hospitalization had been necessary for the relief of their too frequent attacks. In these, the need for adrenalin was gone in about seventy-two hours after the first inhalation. This cannot be interpreted as being due to the benzedrine, but is offered to indicate that the effects of the benzedrine inhalations are not reflected in later exacerbations.

Of the five individuals who did not get relief, two were unable to coordinate sufficiently to inhale deeply through the tube. One refused to inhale after the third inhalation because of the irritation of his throat and bronchi. The fourth had very transient temporary relief, followed within three or four minutes by an exacerbation which was not relieved by additional inhalation. The inhalations were associated with cough, productive of about an ounce of sputum. In the fifteen minutes after his final inhalation, the symptoms became gradually worse. It was finally necessary to give him three injections of adrenalin before he became comfortable. After the third injection of adrenalin, he was more relieved than at any time during the previous two weeks. He continued partially relieved for another week. The fifth unrelieved case tried the inhalations four times for each of three attacks in one night. In each instance, she had to have adrenalin before becoming comfortable. In neither instance was the relief from the adrenalin after the inhalation greater than she had obtained many times before from single doses of adrenalin.

In none of the unrelieved cases nor in any of the side effects was any real contraindication to the use of the drug elicited. It is probably true

that other unpleasant side effects will be elicited with wider use of peroral benzedrine inhalation.

Toxic effects of nasal benzedrine inhalation have been described in detail by Waud.[3] He showed that the toxic dose is significantly greater than the ordinary therapeutic dose. Simpson and Simon[4] showed that forty-eight inhalations were necessary to consume about 2.4 mg. of the drug, a small therapeutic oral dose. The use of benzedrine inhalation is, of course, subject to the same well-known limitations for this and for all other sympathomimetic drugs.

SUMMARY

Peroral inhalations of volatile benzedrine base have been shown to increase the vital capacities of a small group of normal individuals.

Benzedrine inhalations blanch the normal bronchial mucosa visibly. The inflamed bronchial mucosa is blanched and shrunk markedly and aids materially in bronchoscopic inspection.

Benzedrine inhalations are useful in the symptomatic relief of a high percentage of mild and moderately severe paroxysms of asthma. When used in conjunction with adrenalin hypodermically or ephedrine by mouth, it seems to be more efficient than either drug alone. Its effects are roughly comparable to those of the inhalation of 1:100 adrenalin vapor.

Benzedrine inhalation is not helpful in every case.

A typical response, some variations from this typical response, and some of the unpleasant side effects are described. No definite contraindication to benzedrine inhalation was noted in about four hundred inhalations for sixty-nine attacks of asthma.

It is hoped that this preliminary presentation of our experience with peroral benzedrine inhalation will stimulate more general studies of the principles involved and that the uses and limitations of this symptomatic remedy will be more quickly established than if the report were withheld for more detailed study.

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URTICARIA OF BACTERIAL ORIGIN*

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EXPERIMENTALLY it has been shown[1] that an urticarial wheal can be produced not only by the local application of various physical, chemical, and mechanical agents, but also by the infestation of the noxious agent after preliminary sensitization of the skin with serum from a hypersensitive patient. Even though urticaria may result from various causes,[2] it has become increasingly obvious that intrinsic factors, mainly of a bacterial nature, play a very important etiologic rôle, especially in the chronic type of urticaria. It is the purpose of this paper to illustrate this circumstance and to report a therapeutic adjunct which, in some of our cases, has proved valuable.

CASE REPORTS

CASE 1.—F. S. W., aged fifty-seven years, was admitted to the hospital for treatment of pernicious anemia, symptomatically, of one year's duration. There was no familial or personal history of allergic disturbances. Physical examination revealed pallor, emaciation, fresh retinal hemorrhages, absent knee and ankle jerks, and diminished vibratory sense below the hips. The peripheral blood findings were those seen in a severe addisonian anemia. Repeated examinations of the urine during the first two weeks showed nothing abnormal. The blood calcium was 10.5 mg. per cent, phosphorus 3.3 mg. per cent, the refractive index 1.3460. Renal function was normal. During the first three days of observation, the temperature fluctuated between 38° C. and 39.2° C. After liver therapy was instituted the fever subsided and the patient improved steadily, both clinically and hematologically. On the fourteenth day she was allowed to get up preparatory to going home. Two days later she had a sudden chill, followed by the appearance of generalized urticaria. The temperature rose sharply to 40.8° C., accompanied by extreme malaise, nausea, and vomiting. Examination of the urine on this day disclosed numerous white and red blood cells, which were also seen in a specimen obtained when she was cytoscoped. Cultures from the urine gave a pure growth of hemolytic *Staphylococcus aureus*. The patient was treated promptly for her pyelitis, being cystoscoped on several occasions. The temperature subsided by lysis in about eight days. During this time the patient suffered severely from her intense urticaria. She was skin-tested to a large number of streptallergens, staphylococcus toxoid, and to liver extract preparations in varying dilutions, as well as to the common foods. She received no drugs during her hospital stay. She gave a very strong immediate (after thirty minutes) wheal reaction to staphylococcus toxoid but no positive reactions to any of the other allergens. After the urinary infection subsided clinically and the bladder urine cultures showed only a scant growth of *B. coli communior*, the urticaria disappeared. The patient has since been seen on various occasions, and since her discharge from this hospital two years ago has had no recurrence of the urticaria. She is still markedly skin sensitive to staphylococcus toxoid.

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This case illustrates an acute urticaria in an individual, apparently of nonallergic antecedents, occurring in the course of pyelitis. Careful questioning after her recovery revealed that during the preceding year "small amounts of pus" had been found by her physician in her urine from time to time. It seems, therefore, quite probable that she had become sensitized to the infecting organisms and as a result developed urticaria in the course of an acute exacerbation of her chronic pyelitis.

Four other patients have been observed who had their first attack of urticaria in the course of an upper respiratory infection. Two of these were middle-aged women, one a young woman of twenty years, and the other was an elderly man. All four of these patients had a negative family history for allergy. The man stated that he had noticed vague gastrointestinal discomfort; namely, flatulence, eructations, and occasional nausea, for about five years previously, after eating certain vegetables. He was the only one of these four patients who gave positive skin tests to nonbacterial allergens. The average duration of the urticaria in these patients was six months, and in all four the first attack had occurred in the course of a head or chest cold. The site of the infection in all of them was the upper respiratory tract, resulting in a moderately severe suppurative bronchitis, complicated in two by a definite infection of the maxillary and ethmoid sinuses, and in another by a severe tonsillitis. Cultures of the sputum from the patients with active bronchitis gave a variety of organisms, including hemolytic *Staphylococcus aureus*, Beta hemolytic streptococci, and a mixture of anaerobic bacteria. Stool, urine, and duodenal fluid cultures disclosed nothing of significance.

These patients were tested to their respective autogenous vaccines and to staphylococcus toxoid and were found to give an immediate wheal reaction to staphylococcus toxoid and a delayed (twenty-four hours) tuberculin-like reaction to the vaccines. No fungi were obtained from the sputum of any of these patients. All received autogenous vaccine treatments after removal of foci of infection. In the three who were operated upon, the urticaria disappeared within two weeks, and has not recurred in over six months, whereas previously the urticaria had been present almost continuously. The fourth patient, the elderly man with bronchitis, is markedly improved, and is still taking his vaccine. In two of the patients who were subjected to a surgical procedure for the removal of foci of infection, a temporary flare-up of the urticaria, in very severe form, was noted. This was particularly noted in a fifth case; that of a young woman with chronic, intractable urticaria of seven years' duration, where the focus of infection was in a previously undiagnosed peridental abscess. Skin tests showed her to be markedly sensitive to various streptallergens. Following the extraction of the infected tooth, she developed a generalized severe urticaria, complicated

by angioneurotic edema of the eyelids, hands, fingers, and tongue. Cultures from the root of the removed tooth gave Beta hemolytic and Alpha hemolytic streptococci.

In another group of patients suffering from chronic urticaria the infectious process was in the biliary and, probably secondarily, in the gastrointestinal tract. Such individuals present a rather difficult and complex therapeutic problem. Hemolytic bacteria were recovered from the duodenal contents of all of these patients. The almost specific curative effects of prontosil, prontylin, and related compounds in Beta hemolytic streptococcus infections are generally recognized.[3, 4] It was therefore considered worthwhile to observe the effect of these drugs on the suspected causative infection in this group of urticaria sufferers. These observations are exemplified in the record of the following patient:

CASE 2.—A white married housekeeper, forty-one years of age, complained of recurrent urticaria, of seven years' duration. Her family history was negative for allergic disturbances. Her past history disclosed a rather marked predisposition to head and chest colds, and recurrent flatulence and gaseous distention over a period of ten or twelve years, particularly after eating fried or greasy foods. She stated also that six months after the first appearance of the urticaria, she developed an almost constant burning in the lower abdomen which was accentuated by micturition. These symptoms have since recurred in paroxysms and usually only during the height of the urticarial eruption. Cystoscopic examination showed edema and reddening around the vesical orifices, extending far out into the urethra. She gave no other history of symptoms of allergy.

On physical examination she was found to be well developed and a little overweight. Vanishing urticarial wheals were seen on the trunk and lower extremities, with a slight puffiness of the dorsum of both hands. There were no significant abnormalities in the eyes, ears, nose, and throat. The tonsils had been cleanly removed many years previously. The heart and lungs were normal; the blood pressure was 115/70 mm. Hg. On examining the abdomen she complained of considerable tenderness in the right upper quadrant. The abdominal organs were not palpable and no abdominal masses were felt. The peripheral blood findings were normal (no eosinophilia). The urine contained occasional white blood cells. The blood Wassermann and Kahn reactions were negative. Blood chemical studies disclosed nothing of significance. Gastric analysis showed 14° of total acid after histamine but no free HCl. The gallbladder was found to be well filled fourteen hours after the administration of the oral dye. After the fatty meal, however, the x-ray films showed a diminished density and incomplete constriction of the gallbladder, indicating perhaps a low grade infection of this organ. Stool cultures: (Poured plates) Many colonies of hemolytic *B. coli* and Beta hemolytic streptococci. Cultures of material obtained by duodenal drainage: hemolytic *B. coli*, Alpha hemolytic streptococci, and Beta hemolytic streptococci. Urine cultures were sterile. The patient was skin-tested to all of the common inhalants, contact and food allergens with negative results. She was also skin-tested to a large number of streptallergens (tonsillitis, erysipelas, scarlatina strains), staphylococcus toxoid and E. *coli* filtrates. She gave strong immediate (thirty minute) wheal reactions to a few of the streptallergens and also to the staphylococcus toxoid and E. *coli* filtrate. The staphylococcus toxoid was the only allergen which caused delayed tuberculin-like reactions. The patient was then skin-tested to vaccines prepared from the organisms cultured from her stools and duodenal

fluid and gave strong immediate, as well as delayed, reactions to all of these bacterial allergens.

On the assumption that this patient's urticaria was due to an infection in her biliary and gastrointestinal tracts, she was given a course of prontylin, supplemented later by prontosil. The effect on the evidence of her infection and on the skin reactions to various bacterial allergens was quite striking, as shown in the following chart:

CHART I

EFFECT OF PRONTYLIN AND PRONTOSIL ON THE INFECTIOUS PROCESS

DATE	AMOUNT OF PRONTYLIN PRONTOSIL	STOOL CULTURES	DUODENAL FLUID CULTURES	SKIN REACTIONS: (TO VACCINES)*	IMMEDIATE (30 MINUTE)	DELAYED (24 HOUR)
1/9/37	0	Heavy growth B. hem. strep. Hem. E. coli	Heavy growth B. hem. strep. A. hem. strep. Hem. B. coli	B. hem. strep. A. hem. strep. Also skin sensitive to various streptallergens and staph. toxoid	+++ (wheal) ±	++++ 0
1/22 to 1/25	Prontylin 3.5 gm.	B. hem. strep. 1 colony Hem. E. coli 2 colonies A. hem. strep. 6 colonies	B. hem. strep. 3 colonies A. hem. strep. numerous Hem. B. coli 2 colonies			
1/28	0	B. hem. strep. 4 colonies				
1/29	0	A. hem. strep. numerous Hem. E. coli few				
1/29 to 1/30	Prontosil 40 c.c.	B. hem. strep. rare A. hem. strep. occasional Hem. B. coli occasional B. hem. strep. occasional A. hem. strep. numerous Hem. B. coli occasional	B. hem. strep. 0 A. hem. strep. occasional Hem. B. coli 0			
2/2 to 2/6	Prontylin 4.5 gm.	On 2/4 B. hem. strep. 0 A. hem. strep. 10 colonies Hem. E. coli occasional On 2/6 No hemolytic organisms (practically sterile)	No organisms	B. hem. strep. A. hem. strep. Hem. B. coli.	± (no wheal) 0 0	++ + +++

*All skin tests were carried out with a 1:10 dilution of the bacterial allergen.

The patient became free of urticaria after the first course of prontylin. The urinary discomfort gradually abated, particularly after the second course of prontylin. She has been under observation since her discharge from this hospital. Frequent stool and duodenal fluid cultures have shown no hemolytic organisms,

other than the reappearance of Alpha hemolytic streptococci in the stools from time to time. She has been entirely free from urticaria for nearly a year. She has received no prontylin or other drug during this time. During the past six months she has been taking a vaccine prepared from the organisms cultured from her stool and duodenal fluid at the onset of her treatment. She continues to give fairly well marked delayed reactions to these bacterial allergens, as well as to a number of streptallergens and staphylococcus toxoid, but has failed to show immediate wheal reactions to any of these substances, except staphylococcus toxoid, since the completion of the first course of prontylin.

We have observed four other patients in whom very similar relationships were noted. In all of these the hemolytic organisms disappeared from the stools and duodenal fluid after a course of prontylin or its derivatives. All of these patients lost their immediate skin reactivity to their respective streptallergens with the cessation of the acute urticaria. Three of the patients have been free from urticaria for more than four months, after an average duration of three years of the eruption.

DISCUSSION

Although the mechanism of the production of the urticarial wheal, as well as the immediate circumstances which result in an urticarial eruption, still remains unexplained, clinical and laboratory investigations have demonstrated the etiologic importance of bacterial infections in this allergic disturbance. It would be hazardous to assume that such infections are the only precipitating causes of urticaria, since there are undoubtedly instances in which the most careful study will fail to reveal evidences of infection. On the other hand, we have become convinced that in the adult, urticaria is usually present in conjunction with an infection. Careful questioning of such patients will often reveal a predisposition to colds, the existence of dental trouble or some other possible focus of infection. Careful examination may disclose unsuspected infection in the teeth or sinuses. The vast majority of individuals suffering from an acute infection do not show urticaria or angioneurotic edema. One must assume, therefore, that patients who show urticaria under these conditions do so because of an inherent, underlying physiologic disturbance which allows them to become sensitized to bacterial products.

The predominating infective organism in our cases was the Beta hemolytic streptococcus. It has long been known that individuals can become sensitized to products of this organism. Positive skin reactions to filtrates of hemolytic streptococci have been obtained in patients suffering from a variety of Beta hemolytic streptococcus infections.[5] Although a positive skin reaction does not necessarily imply a somatic hypersensitivity, it should be remembered that in Beta hemolytic streptococcus infection the skin reactivity parallels fairly closely the severity of the infection, particularly in supposedly allergic individuals. The

close relationship between infection and urticaria in our patients was furthermore suggested by the cessation of the acute attack of urticaria, after a preliminary exacerbation, following the eradication of the infection. In the five cases in which the focus was suspected to be in the gastrointestinal and biliary tracts, stool and duodenal fluid cultures showed large numbers of Beta hemolytic streptococcus colonies. They were all of the "large" variety, and no "minute" hemolytic streptococci were seen.[6] These patients were treated with prontylin, prontosil, or sulfanilamide. In all but one of these individuals the stools and duodenal fluid contents became promptly free from Beta hemolytic streptococci after treatment. These drugs did not seem to affect materially the presence of Alpha hemolytic streptococci. In view of the fact that the urticaria subsided soon after the disappearance of the Beta hemolytic streptococci, even though Alpha hemolytic streptococci could still be grown, it is believed that the first named organisms play the important causative rôle. It should be stated that eosinophilia was present in only two of these groups of patients, and was then only of a slight or moderate degree (maximum 9 per cent). This might possibly be considered a differential feature to distinguish between this group of urticaria and that due to food sensitivity. As will be noted from the above chart, the patient's skin, very soon after the administration of prontylin, lost the faculty of giving immediate wheal reactions to the Beta hemolytic streptococcus vaccine. The delayed tuberculin-like reaction was not influenced. We have observed this phenomenon in three other patients, but at present can offer no explanation.

CONCLUSIONS

1. Bacterial infections were demonstrated either in the upper respiratory tract, bronchial tree, or duodenal contents of ten adults suffering from urticaria.

2. Beta hemolytic streptococci were cultured from all of these patients, and were often the predominating organisms.

3. These patients were found to be skin-sensitive to streptallergens and autogenous vaccines.

4. Elimination of the infection was followed in every case by the subsidence or complete disappearance of the urticaria.

5. The administration of prontylin, prontosil, or sulfanilamide resulted in the disappearance of Beta hemolytic organisms from the stool and duodenal juice. The growth of Alpha hemolytic organisms in the stool and duodenal fluid cultures was not influenced by these drugs.

6. The patients who received prontylin or allied compounds, lost their immediate (thirty minute) wheal reactions to their autogenous (Beta hemolytic) streptococcus vaccine.

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URTICARIA OF THE SERUM SICKNESS TYPE*

Report of Five Cases

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MOST clinicians agree that the allergic management of urticaria has not been satisfactory. Only a relatively small percentage of urticaria patients give positive skin reactions; eliminative measures, as well as hyposensitization treatment, have been largely disappointing.[1-3]

The poor response to skin testing can be partly explained by the high incidence of causative factors for which skin reactions are either not satisfactory or unobtainable, such as bacterial infections, drug sensitivity, and heat and cold. Stokes, Kulchar, and Pillsbury[4] believe in a neurogenic basis for certain types of urticaria. In spite of such explanations for the failure of the allergic regime in urticaria, we have felt for some time that in a large percentage of cases there is altogether too little evidence to warrant its consideration as an allergic disease. The question arises whether or not there are two types of urticaria, one which presents the common criteria of allergy, and one which cannot be considered as atopic.

This thought is more forcibly brought to mind if we review briefly how urticaria originates in man. It is true, experimental production of chronic urticaria has yet to be established; however, it is relatively easy to produce acute urticarial wheals artificially. They may or may not be associated with other symptoms; they may either be localized or, if a marked excess of antigen is used, they may appear generalized.

The injection of an antigen, such as horse serum, may result in two distinct types of urticaria depending on whether or not the individual is sensitive to horse serum: in a sensitive patient it results in a localized wheal (skin test); if an amount above the individual's threshold of tolerance is given it results in allergic shock. In the nonallergic patient, or in the allergic patient not previously sensitive to horse serum, it may, under certain conditions, result in urticaria associated with serum sickness.

THE ALLERGIC WHEAL

There is no need of discussing the allergic type of urticaria. Suffice it to recall that the wheal of allergic urticaria can be brought on not only by injection of an antigen into the sensitive skin, but also by passive transfer of atopic serum into a nonallergic recipient and injection of

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the respective antigen into the sensitized site. Reinjection,[5] inhalation,[6] and ingestion[7] of the same or any other antigen to which sensitivity exists may cause an urticarial wheal to flare up either in the sensitive individual's skin or at the site of the passive transfer. In all these instances the intensity of the wheal depends largely on the degree of sensitivity and the dose of the antigen.

URTICARIA IN SERUM SICKNESS

If the individual is not sensitive to horse serum, regardless of whether or not he is allergic, the injection of the horse serum does not result in either an immediate wheal or in an immediate generalized urticaria. Instead, a so-called late reaction of the serum sickness type is often encountered. It has been stated by Coca, Deibert, and Menger[8] that it is possible to produce this type of reaction in 90 per cent of normal individuals, this percentage being proportionate to the size of the dose administered. Certain antigens, such as pseudoglobulin, are more apt to produce serum sickness than others.[9] In serum sickness the urticaria is usually generalized, but it may also be localized.[10] This type of urticaria is not associated with allergic symptoms as appear in the type described above, but it occurs in conjunction with such nonallergic symptoms as arthralgia, glandular swelling, and fever. A review of the features distinguishing serum sickness from allergic shock is given in Table I.

TABLE I

DISTINCTION BETWEEN "ALLERGIC" SHOCK AND SERUM SICKNESS

	OCCURS IN	INCUBATION TIME		SYMPTOMS	RESULTS
"Allergic" shock	Only sensitive individuals	From a few minutes to 24 hours	URTICARIA	*Only allergic* Sneezing Coughing Wheezing Vomiting Diarrhea Convulsions, etc.	Decrease of previous state of sensitization
Serum sickness	Sensitive and non-sensitive	5 to 12 days	URTICARIA	*Simulating acute infections* Fever Joint swelling Glandular enlargement Malaise, etc.	Probably more sensitive

The immunologic significance of serum sickness is not clear at the present time. Cooke and Spain,[11] as well as Tuft and Ramsdell[12] found passive-transferable reagins most pronounced between the third and fourteenth days after the onset of serum sickness. Anaphylactic antibodies were also found by the latter authors. Gordon and Creswell[13] showed that skin tests which had been negative before serum sickness were positive afterwards. This, however, has not been confirmed. We

have personally observed several patients who developed serum sickness after a first injection of horse serum; subsequent injections resulted in allergic shock. All these observations suggest that there may be either a freshly established, or at least an increased, sensitivity to the antigen administered as a result of serum sickness. However, such sensitivity is not likely to be permanent.

In the literature on urticaria no reference could be found which indicates that the mechanism of serum sickness may be at play in the production of clinical urticaria. Hopkins and Kesten[3] give an excellent review of the characteristics of urticaria in serum sickness. While they hold serum sickness responsible for certain cases of clinical urticaria, they present no evidence that urticaria of the serum sickness type may be produced by means other than injections. Coca[14] comments on a case of a "drug rash" which appeared eight days after the injection of novocain and suggests its identity with serum sickness.

We wish to present five cases which are representative of the serum sickness type of urticaria and which illustrate certain characteristic features of this condition.

CASE REPORTS

CASE 1.—M. W., a nine-year-old boy, was first seen December 16, 1931, with chronic urticaria. Nine months before admission, 1 c.c. of toxin-antitoxin had been given after he previously had had a positive Schick test. The toxin-antitoxin had been prepared from horse serum. On March 3, 1931, six days following the injection, a localized urticaria had appeared at the site of administration and had spread within twelve hours over the entire body. Marked pain and edema of the knees and ankle joints, a maximum temperature of 102°, general malaise, and anorexia had accompanied this condition and had persisted for about five days. The urticaria, however, continued with the same severity for nine months in spite of a large array of local and general therapeutic measures.

When first seen, rather complete intradermal and passive transfer tests with some of the more important antigens were made, including Schick test material, normal horse serum, and diphtheria toxin-antitoxin. They were all negative with the one exception of a marked wheal with pseudopods for toxin-antitoxin. Passive transfer on two normal subjects who had not previously had toxin-antitoxin gave two- to three-plus reactions. The patient was given an injection of 0.1 c.c. of a 1:1000 dilution of toxin-antitoxin. This resulted in considerable improvement of the urticaria. During the following days these minute doses of toxin-antitoxin were increased, and the urticaria disappeared entirely on the third day. Skin tests and passive transfer tests performed six weeks after the disappearance of the urticaria were negative.

Comment.—This case illustrates an instance of chronic urticaria due to serum sickness as a result of administration of toxin-antitoxin, and its prompt response to a few small desensitizing injections after other nonspecific measures had failed. It is of particular interest that the skin and passive transfer reactions became negative after six weeks.

CASE 2.—J. D., a thirty-nine-year-old male. (This case has been described in detail elsewhere.[15]) Chronic urticaria had been present for four years, appearing at a remarkably regular periodicity of six weeks and lasting about three to five days. The patient also had hay fever and gave a large number of two- to four-plus reac-

tions to foods, epidermals, and pollens. While specific hyposensitization and eliminative procedures improved the hay fever, the urticaria failed to respond. Nonspecific therapy, including injections of histamine, vaccine, and milk was equally unsuccessful. The patient had been under observation for nearly a year when it became evident that at periodic intervals, between five and nine days before the onset of the hives, lesions typical of epidermatophytosis appeared on the feet. An autogenous fungus extract gave a three-plus reaction while other control tests for fungi were negative. As soon as the lesions were controlled by local and specific therapy, the urticaria cleared up. Incidentally, it was noted that every six weeks, immediately before the onset of urticaria, the regular pollen injections for hay fever produced marked generalized reactions in spite of a considerable decrease in doses. During the past year there were two seizures of urticaria, occurring again seven and eight days, respectively, after the recurrence of the ringworm infection. No treatment had recently been given.

Comment.—The six weeks' periodicity, the regular appearance and disappearance of the fungus infection about one week before the onset of urticaria, as well as the prompt response to specific desensitization, are of interest in this case.

CASE 3.—T. J. R., a thirty-year-old dentist, was seen on April 26, 1933, because of a generalized angioneurotic edema which had been present for three weeks. At the onset, the lesions were associated with a temperature of 99.5° and pains in knees and elbow joints. The attacks occurred practically every day, with no apparent relationship to foods, air-borne substances, or contactants. No history of personal or familial allergy was elicited. No unusual physical signs other than those of angioneurotic edema were present. Intradermal skin tests were negative with the exception of a few questionable reactions to fish. There was no eosinophilia in three successive blood smears. Nonspecific therapy, including injections of histamine, the pollen prevalent in the air at that time, peptone, and autohemotherapy were tried without affecting the skin lesions. While under our observation, the patient had been taking tablets of acetylsalicylic acid occasionally because of the arthralgia. After this medication was discontinued, the skin condition persisted for eight days and then disappeared entirely. About six weeks later, one grain of acetylsalicylic acid was administered to the patient without his knowledge as a clinical test. This resulted within ten minutes in a severe outbreak of urticaria. Scratch and patch tests, however, were negative. When the patient was informed of his sensitivity he stated that, to his knowledge, he had not taken this drug, either alone, or in combination with others, at least during the past ten years, until March 28, 1933, his birthday, when he took two tablets in order to relieve a severe headache. This was eight days before the onset of the urticaria.

Comment.—We have noted that urticaria due to drugs is not infrequently preceded by an incubation period. In this case the history of the incubation period suggests that the urticaria was originally of the serum sickness type; after its first occurrence, however, it did not present features distinguishable from the allergic type, the patient apparently having become sensitive to the antigen.

CASE 4.—Mrs. L. L., aged fifty-three years, was seen at her home December 28, 1936, because of severe urticaria, chiefly on the face, but also involving the entire body surface. This had been present for twelve hours; there were marked joint pains and a temperature of 102°. No personal or familial history of allergy was determined. Six days previously the patient had had an acute tonsillitis which had been treated by gargles and application of argyrol. The patient stated that no internal medication had been taken. A white blood count taken on the first day of the urticaria showed a leucocytosis of 16,200, 87 per cent neutrophiles and 13 per cent small and large lymphocytes. Several injections of epinephrine (0.2 to 0.7 c.c.)

TABLE II

HORSE SERUM INJECTED					SKIN AND PRAUSNITZ-KÜSTNER REACTIONS FOLLOWING THE ONSET OF SERUM SICKNESS						
NO.	INITIALS	DATE	AMOUNT	ONSET OF SERUM SICKNESS	1ST DAY	3 DAYS	1 WEEK	2 WEEKS	3 WEEKS	1 MONTH	6 MONTHS
1.	S. H.	4/9/36	40 c.c.	4/16/36	–	–*	++			+++	+
						(–)†	(+)			(++)	(+)
2.	R. T.	4/23/36	20 c.c.	4/28/36		+++	++++		+		–
							(++)		(?)		(–)
3.	S. W.	5/2/36	10 c.c.	5/7/36			++		++	+	
							(++)		(–)	(–)	
4.	O. R.	6/3/36	20 c.c.	6/10/36	?		+++		+++		++
							(++)				(+)
5.	W. K.	6/24/36	20 c.c.	6/30/36			++	++		–	
							(–)	(–)			
6.	O. L.	7/4/36	30 c.c.	7/11/36			++	++	++	–	
							(+)		(+)	(–)	
7.	E. N.	7/8/36	40 c.c.	7/15/36		++	+++		+		–
						(++)	(++)				
8.	G. L.	8/2/36	20 c.c.	8/10/36			++		–		
9.	I. G.	9/23/36	20 c.c.	9/28/36		+++	+++	++	–		
						(+)					
10.	C. E.	10/6/36	30 c.c.	10/12/36			++				
							(–)				
11.	L. O.	10/23/36	40 c.c.	10/30/36	–		+++	++++	+++		
							(–)	(++)	(+)		–

*Skin Tests.
†Prausnitz-Küstner Reactions (in parentheses).

gave only slight symptomatic relief. The temperature and joint pains subsided after three days, but the urticaria persisted for eight weeks during which time such therapeutic measures as small doses of a respiratory stock vaccine were of no avail.

Complete intradermal skin tests were negative except for questionable reactions without pseudopods to *Staphylococcus aureus, Streptococcus hemolyticus,* and *Micrococcus catarrhalis.* On March 2, an autogenous vaccine was made from material expressed from the tonsils which, in addition to the above named bacteria, included Pneumococcus, type I. An intradermal injection of this autogenous vaccine resulted in a rather marked local response. Passive transfer of these bacterial reactions, however, was unsuccessful. The urticaria disappeared shortly after this injection.

Comment.—We observed other cases of acute infections followed within about one week by urticaria, but we were not able to substantiate the causal relationship as clearly as in this patient.

CASE 5.—Mrs. R. S., aged thirty-five years, consulted us because of a contact dermatitis involving the face and the upper portion of the neck, present for nine months. There was no allergic family or personal history. Intradermal tests were uniformly negative. Patch tests were positive to olibanum, a resin which was present in her hair lotion, and to a certain soap, which she employed exclusively. The reaction to the latter material was only mild, but the site of the patch test failed to clear up in spite of the removal of the soap. On the eighth day, the site became markedly pruritic, and this was followed shortly by a generalized urticaria. At the height of this condition, the patient had a temperature of 100.2°, some inguinal adenopathy on the side which was patch tested, and general malaise. A white blood count showed 9,800 cells with no eosinophiles. After ten days this condition gradually subsided. A check on the patch tests performed four weeks afterwards revealed a four-plus reaction for the soap, much more marked than before, yet promptly subsiding two days after removal of the patch test.

Comment.—The incubation period, the fever, and adenopathy suggest a mechanism similar to or identical with serum sickness, despite the fact that only superficial contact of the antigen had taken place. Here also an enhancement in sensitivity had apparently taken place during the course of the urticaria as shown by the stronger positive patch test reaction.

DISCUSSION

Although the serum sickness type of urticaria is probably not infrequent, it is impossible to present data as to its incidence because of the great difficulties encountered in establishing the antigenic relationship in such cases. In the patients reported here, the chief diagnostic aids were the definite history of the typical incubation period, the coexistence of other symptoms characteristic of serum sickness, and relief following specific treatment when nonspecific measures had previously failed. A mechanism of this form of urticaria distinct from atopy is particularly suggestive in Case 2 where other symptoms, which were definitely allergic, coexisted. While the control of the allergic factors relieved the allergic condition, the urticaria could not be influenced by allergic management.

In the differential diagnosis of urticaria of the serum sickness type the following should be emphasized:

1. *History.*—The time interval between contact with the antigen and the appearance of symptoms, which is from five to twelve days, is

undoubtedly the most significant clinical feature. This incubation period should not be confused with the one to two days' interval indicative of a delayed allergic reaction. Furthermore, it should be recalled that serum sickness occurs in allergic as well as in nonallergic individuals. A family and personal history of allergy, therefore, may or may not be present.

2. *Skin tests.*—Inasmuch as the data on skin testing in serum sickness are rather inconclusive, we studied intradermal and passive transfer tests on patients who developed serum sickness after therapeutic injections of horse serum.* Table II shows the results of serial skin and passive transfer tests in 11 such cases. The skin reactivity appeared to be strongest from two to six weeks after the therapeutic injection, and in two patients persisted for more than six months. There was no appreciable difference in the results of the passive transfer tests as compared to the intradermal skin tests. These results corroborate the findings of Tuft and Ramsdell[12] and indicate that serum sickness may be instrumental in setting up a sensitivity which may be of a more or less extensive duration. In clinical urticaria of the serum sickness type, therefore, one may obtain positive skin reactions, yet such finding is not obligatory.

In only 22 per cent of 168 consecutive cases of urticaria there was exhibited what can be termed a satisfactory response to skin testing, i. e., two- to four-plus reactions. This lack of skin reactivity may in part be accounted for by the fact that some of the nonreacting cases are of the serum sickness type of urticaria in which only a single antigen can be expected to be causative and at certain times no reactions are obtainable.

3. *Eosinophilia.*—This, we believe, is another diagnostic feature. In 16 consecutive cases of serum sickness following the injection of horse serum, the eosinophil count averaged 0.72 and the white blood count 11,250 at the height of the serum sickness. This differs appreciably from the eosinophilia which is usually encountered in allergic shock.[16] Assuming, therefore, that the eosinophil count may well serve in the differentiation of the allergic and the serum sickness types of urticaria, we studied the eosinophil count in our series of 168 cases of urticaria. Among those who gave positive skin reactions the eosinophilia averaged 3.4 per cent; among those whose skin reactions were negative, 0.78 per cent.

4. *Clinical behavior.*—The association with other symptoms encountered in serum sickness; namely, fever, malaise, glandular and joint disturbances, may further serve as a differential diagnostic criterion, while the presence of allergic manifestations such as nasal and gastrointestinal atopy points to the allergic type of urticaria.

*For the information on some of these we are indebted to Dr. D. C. Young of Herman Kiefer Hospital in Detroit.

It is of practical importance to recognize the serum sickness type of urticaria for the following reasons: If the relatively long incubation period is borne in mind the causative antigen can be more readily detected. Inasmuch as usually only a single antigen is responsible for serum sickness, more reliance, in general, will have to be placed on the history than on any other diagnostic procedure. A great deal of unnecessary skin testing can, therefore, be avoided, particularly if we bear in mind that skin tests in the serum sickness type of urticaria are of rather limited value. In the therapy of urticaria of the serum sickness type the elimination of the antigen does not appear to be as successful as in allergic urticaria. Such elimination may already have taken place before urticaria develops, as in Case 1. Specific desensitization, on the other hand, has been very helpful in our cases.

SUMMARY

1. In five cases of urticaria a definite incubation period of five to nine days was noted and manifestations such as fever, joint and glandular swelling were present which are indicative of serum sickness.

2. In four of five cases this condition was brought about by means other than injection; namely, ingestion, contact, and infection.

3. For the purpose of differentiating between the serum sickness type and the allergic type of urticaria the clinical characteristics of serum sickness were investigated and the following criteria were noted:

a. In serum sickness the skin reactivity appears to be of a transitory character. This is indicated by the results of skin and passive transfer tests in 11 patients of serum sickness following injection of horse serum.

b. No eosinophilia was present in 16 consecutive cases of serum sickness following injections of horse serum.

c. The characteristic incubation period and the presence of symptoms usually associated with serum sickness are of diagnostic significance.

4. In a survey of 168 consecutive cases of urticaria, only 22 per cent gave satisfactory skin reactions. Considering the great difficulties encountered in making the diagnosis of urticaria of the serum sickness type, and, on the other hand, the questionable skin reactivity in such cases, we believe that the incidence of this condition may not be uncommon.

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10 PETERBORO.

Special Reports

RETENTION OF LIPIODOL IN THE LUNGS*

With Two Case Reports

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DURING the last decade roentgen-opaque substances as contrast media for injection into the subarachnoid space, the Fallopian tube, the spinal cord, and other body cavities have been widely used for diagnostic purposes. That such use of iodized oils has been attended with complications and sequelae, some slight, others serious, has been noted by a number of observers. In a recent article, Rubin[1] discussed the complications from residues of contrast oil and cited several cases demonstrating occlusive and untoward effects from Fallopian tube retention. Disadvantages and dangers of iodized oils have been recognized to such an extent that in 1932, the Council on Pharmacy and Chemistry of the American Medical Association made a report[2] on them. They stated: "As the absorption of oils is extremely slow, some of the material tends to remain indefinitely, especially in closed cavities and to act at least mechanically as a foreign body."

It may be said that injections of lipiodol and other iodized oils into the bronchi for therapeutic as well as diagnostic effect are usually well tolerated as shown by the many favorable reports in the literature. In 1926, Prichard, White, and Gordon,[3] in a study of more than 600 bronchial injections of iodized oil in the diagnosis and treatment of bronchial affections, observed no ill effects and made no mention of retention of oil in any case. In reporting tracheobronchial instillation in more than 1,500 instances of bronchitis and bronchiectasis, Ochsner[4] wrote only of the improvement that followed and of its definite and distinct therapeutic value. Alison[5] reported 10 cases of asthmatic bronchitis, and Harris and Turkel[6] 50 cases of bronchial asthma similarly managed; they mentioned no instance of retention. Over a period of fourteen months, Balyeat, Seyler, and Shoemaker[7] treated 184 asthmatic patients of various types by iodized oil intratracheally or transnasally, without untoward effects. Cole and Harper[8] have 7 illustrative cases of pulmonary disease in which iodized oil was used therapeutically without reference to retention in any case. In one case, according to their report, more than 100 c.c. of iodized oil was introduced within ten weeks,

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with spectacular improvement. Writing of the treatment of 260 cases of bronchial asthma by intratracheal injection of iodized oil, Anderson,[9] of Western Pennsylvania Hospital, stated: "The oil has been kept constantly in the lungs in some patients for three years and a roentgen-ray examination, made 2 years after treatment was discontinued, disclosed no injury to the lung tissue." On one patient with bronchial asthma who died of an abdominal condition, an autopsy study was made. She had received injections of iodized oil for eight months. No pathologic change that could be attributed to the oil was revealed in a study of the lungs. He also referred to roentgenograms of 7 patients who recovered from bronchopneumonia and lobar pneumonia which showed much oil in both lungs. There were, in his experience, no cases of edema, pleurisy, emphysema, or lung abscess following treatment.

Many unfavorable reports have also appeared in the literature. In 1933 Amberson and Riggins[10] stressed the fact that once lipiodol had entered the terminal bronchioles and alveoli, part of it is retained usually for weeks and sometimes for many months. These authors reviewed a series of cases with bad results and fatalities following injection and noted retention of the oil in 5 cases. They ventured the opinion that pneumonic complication is a more common experience than the literature reveals.

Wright[11] observed the retention of oil in the lung of a patient into whose bronchi lipiodol had been instilled twelve months previously. Roentgenograms taken a week before death showed the lipiodol still present in the bronchiectatic cavities, occlusion of the main bronchus being due to epithelioma.

In a recent attempt to gain a consensus of opinion regarding the value of iodized oil in the treatment of asthma, Criep and Hampsey[12] sent out questionnaires to 335 physicians interested in allergy. Replies from 250 indicated that 1205 asthmatic patients were treated with the oil by 64 physicians. Only one-third of the physicians still continue its use. In the 1205 cases, the results, in the opinion of the physicians, showed less than 2 per cent cures, 23 per cent improved, and 75 per cent failures. Fatality due to introduction of the oil was reported in 2 cases.

This analysis conforms closely to our own experience. At this Allergy Clinic, lipiodol was used in a group of asthmatics that failed to improve under routine care. None of these patients received more than a few instillations. At best, a very small percentage of cases were only temporarily relieved. In not a single case have we been able to find a result which approaches what might be considered a "cure."

The following two cases showed a retention of oil in the pulmonary alveoli for many months after instillation; their exceptionally long and stormy course was attributed in large part to the retained oil or its secondary pneumonitis.

CASE REPORTS

CASE 1.—J. L., aged 30 years, an insurance clerk, was admitted to the clinic in January, 1937. Except for an attack of influenza in 1918, his history was practically negative until 1931, when a tonsillectomy and adenoidectomy were performed. In 1934, he began to show symptoms of sneezing, nasal obstruction, and discharge but no cough. Local nasal treatment was given without relief. In 1935, because of the rhinitis, cutaneous tests, made at another clinic, showed sensitivity to pepper and chocolate only. The symptoms continued despite the removal of polyps and adenoids. In March, 1936, because of lack of improvement, phenol cauterization of the nose was done. A few days later the patient began to wheeze and had acute attacks of asthma for the first time. His condition grew worse and in April he was

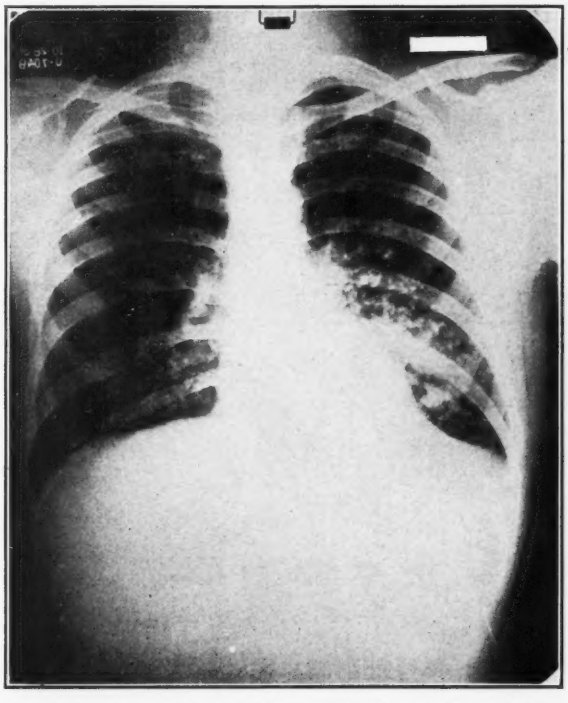

Fig. 1.—Shadows of opaque substance with surrounding inflammatory reaction at the bases of both lungs.

hospitalized for four weeks, with very slight improvement, and throughout that summer he was continuously asthmatic. He was given codeine and adrenalin daily and at times required an oxygen tent. In August turbinectomy was done and he was given four instillations of lipiodol at intervals of a week with no improvement. In December, 1936, he was sent south where his symptoms continued without improvement.

The patient was first admitted to our clinic on January 15, 1937. He was acutely asthmatic and was taking adrenalin injections many times daily. The tests with inhalants and foods gave no positive reactions. The roentgenograms (Fig. 1), which had been taken in October, 1936, revealed pansinusitis and shadows of opaque substance, with surrounding inflammatory reaction at the bases of both lungs. Nasal examination confirmed the presence of pansinusitis with polyposis. New roentgenograms taken (January, 1937) showed the same condition in the sinuses as previously,

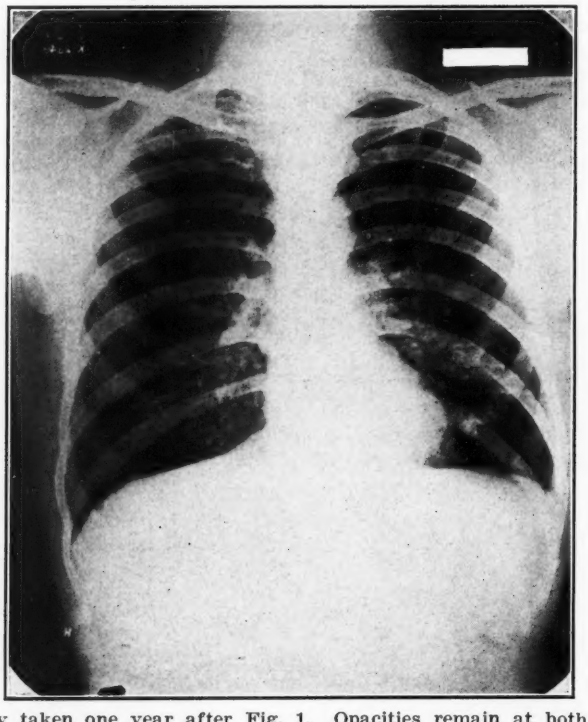

Fig. 2.—X-ray taken one year after Fig. 1. Opacities remain at both bases, more marked at left.

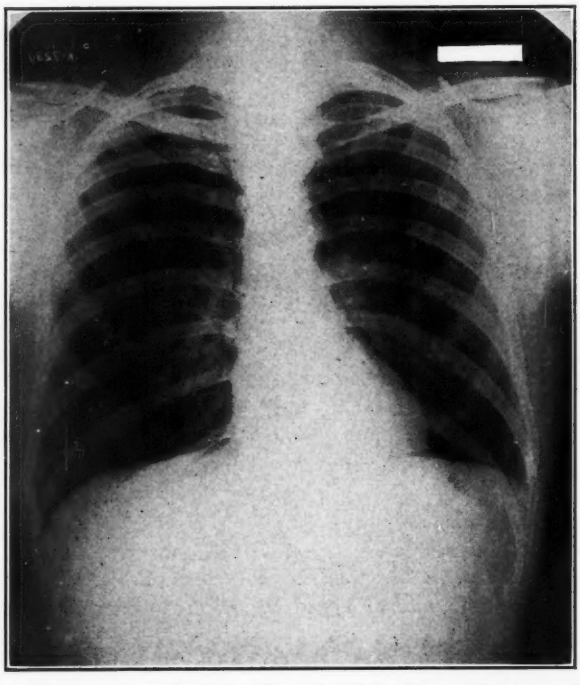

Fig. 3.—Same patient six months after Fig. 2. Opacities and signs of inflammation gone.

and the oil still present in both bases, with an especially large accumulation in the lower left base, resembling a localized patch of pneumonitis. Because of the acuteness of his condition on January 26, 1937, he was admitted to the hospital, where on February 8, 1937, bilateral ethmoidectomy was done. On February 23, a radical left antrectomy was performed. On February 25, the patient complained of headache. He was given aspirin (5 gr.), following which he had a severe attack of asthma, requiring adrenalin injections and the oxygen tent. During his stay the temperature, pulse, and respiration rate were quite normal. Injections of adrenalin continued several times a day. Occasionally amytal or codeine was given. Although he had the benefit of radical nasal surgery, change in environment and general care, he continued to be acutely ill. Roentgenograms in March, 1937 (one year after lipiodol, Fig. 2) showed the same opacities in both bases, with pneumonitis

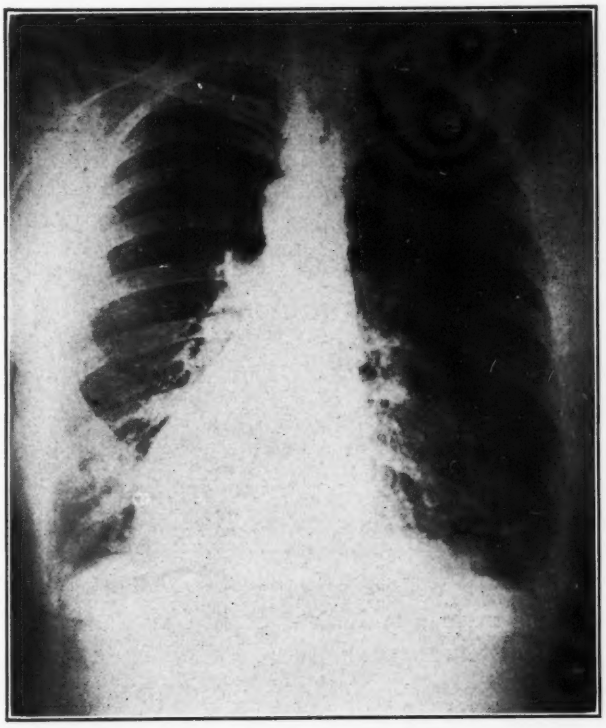

Fig. 4.—Lipiodol retention with surrounding pneumonitis.

more marked in the left base. He was sent to the country for the summer and returned to us in September, 1937. New x-rays of chest now revealed a complete disappearance of the lipiodol and surrounding areas of pneumonitis (Fig. 3). Coincidentally his asthma was improved.

CASE 2.—M. B. K., aged 58 years, came for consultation on July 27, 1933, because of nonseasonal asthma of four years' duration. The family history disclosed her son and niece as having hay fever. The patient's present illness, asthma, began after a "cold" in September, 1929. Following an automobile accident in September, 1931, it recurred and in November, 1931, she was hospitalized without relief. Artificial heat therapy proved ineffective and she was given a single instillation of lipiodol in the bronchi. Asthma was continuous with exacerbation. In September, 1932, another instillation was given and repeated in a week. After each of the three lipiodol instillations, there were symptoms of iodism, swelling of the feet, and

severe asthma for several weeks. In September, 1932, polyps were removed. In December of the same year double antrotomy was performed, affording no relief.

She came under our care on July 27, 1933. Roentgenograms showed shadows in both bases due to lipiodol previously (nearly two years) injected. The right base revealed pronounced markings and the left showed a greater accumulation of lipiodol than the right side, with areas of congestion and consolidation around the opacities. There was no sensitivity to foods, but aspirin and pyramidon produced a violent asthmatic exacerbation. Skin test gave a moderate reaction to dust. Clinical examination showed typical chest symptoms of asthma and emphysema. The heart was normal. The nasal mucous membrane was pale and not much swollen. The right antrum was cloudy; the left, clear. The right orifice was polypoid and the wall inflamed. Washing of the antra yielded mucopus from both sides. On July 31, 1933, the patient was sent to the hospital, where as a result of washing of the antra and rest, she felt better. It was decided to do a radical operation on the sinuses. On August 10, 1933, this was done and bilateral polypi were removed.

On September 19, 1933, roentgenograms of the chest (Fig. 4) showed the same dense shadows in both bases, more pronounced on the right side. It was diagnosed as lipiodol, with secondary pneumonitis.

On September 30, 1933, she left the hospital in an improved condition but this lasted only a short time. On her return home she became progressively worse and died on March 7, 1935, during a paroxysm of asthma.

DISCUSSION

Two cases are presented in which there was, for a considerable period of time, retention of iodized oil in the lungs. There were areas of pneumonitis surrounding the residual oil. The continuation and severity of the asthma were attributed to the secondary pneumonitis.

Two kinds of ill effects from the use of bronchial instillation of iodized oils are illustrated in these cases. The one arises from sensitivity to iodine, in which the symptoms appear promptly and may be mild, consisting only of increased salivation and rash, or they may be severe enough to produce asthma and edema as in Case 2. Deaths have been reported in such instances. The other ill effect is due to foreign body reaction and its clinical effect on the asthmatic state. Both of the cases cited show this second form of untoward effect.

In the first case presented, although all the accepted modes of treatment had been used and radical sinus surgery done, the patient was gradually growing worse, there was no abatement of asthma, and his condition continued to keep him hospitalized for an unusual period of time. It is fair to assume that the retention of lipiodol in the lungs, with the secondary pneumonitis, was an important factor contributing to the severity and duration of asthma. This is supported by the fact that the disappearance of the lipiodol and the pneumonitis, as recently shown by x-ray, was associated with improvement in clinical symptoms.

In the second case lipiodol with accompanying areas of pneumonitis was found present in the lungs after two years, with symptoms becoming progressively worse in spite of all treatment. Here again it seems

probable that the retained lipiodol in both bases acted as an irritant responsible for the continuous asthma which eventuated in death.

Why in one case oil is retained in the lungs for weeks and months and in another case is eliminated within a few weeks has been the subject of some thought. Certain factors are evident. After being instilled in the bronchi, the oil finally seeps down into the smaller bronchioles. In the asthmatic the lumen of the bronchi is narrowed because of the edema of the mucous membrane. Some of this oil is expelled by coughing, but on account of the narrowed bronchial lumen, part of it is forced into the alveoli, where it then remains for an indefinite length of time resulting in irritant action. There may be slight absorption of the instilled substance but apparently most of it must be discharged through the bronchi. This view is concurred in by Amberson and Riggins,[10] Sergent and Cottentot,[13] Knipping and Ponndorf,[14] and Grill.[15]

The effect on the alveolar tissue of retained lipiodol and other iodized oils has been the subject of investigation. Wright[11] considered the reaction to lipiodol retained for long periods to be due to the development of lipophages from supporting connective tissue, no epithelial reaction occurring. Some authors believe the therapeutic advantage of the oil is due to the slow rate of absorption of the iodine. Apparently, the iodine set free in the bronchial tubes becomes sodium and potassium iodide instantaneously. Whether any of the iodine is broken up in the alveolar tissue and liberated still remains undetermined. It seems more likely that the benefit derived from this form of treatment is due to the temporary displacement of the thick tenacious material present in the bronchi. If our concepts of the causation of asthma are correct, a cure cannot be expected from local treatment for a condition that is due to a state of hypersensitivity.

How frequently these complications occur is difficult to estimate. Our only means of diagnosing retention is by the use of x-ray. The opacities of lipiodol seen on the roentgenograph are due to the iodine and not to the oil itself. Although iodized oil is a stable compound, evidence that it liberates iodine is definitely shown by the allergic reaction to iodine in the sensitive case. It seems likely that after the iodine is entirely liberated there may still be a retention of oil not revealed by roentgenographic examination. How long it is retained and what ultimate effect it has on the lung tissue cannot be definitely ascertained until some of these cases come to the autopsy table.

In view of these and similar recorded observations, one should be extremely careful in recommending the use of iodized oil in asthma. A foreign body is being introduced. Its modus operandi is not known and the frequency of retention is uncertain, but when it occurs, secondary pneumonitis may bring serious effects. It is questionable whether one can point to any single case of "cure" from its use, and the percentage showing temporary benefit is small.

SUMMARY

1. Two cases with retention of lipiodol in the lungs of asthmatic patients are reported.

2. In view of the contradictory results in the many cases reported in the literature, use of iodized oils cannot be accepted as a reliable method of treatment in asthma.

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SOYBEAN SENSITIVITY WITH A CASE REPORT*

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THE number of uses for the soybean has increased rapidly in the past twenty years because of the ease of harvesting, the prolific yield, and the demand for its products. The crop increased from 2,500,000 bushels in 1924[1] to 39,637,000 bushels in 1935.[2] New uses in industry and foodstuffs are being found constantly.

The uses of the soybean are roughly divided into three groups: the whole bean, the oil, and the meal. The whole beans are cooked and eaten as a vegetable. They are dried, roasted, and eaten like salted peanuts. When ground and roasted, they form a good cereal coffee substitute. When placed in water and soaked, sprouts develop which are used as a vegetable and form an excellent addition to salads.[3]

The oil comprises 17 to 20 per cent of the bean and is pressed out or is removed by the use of suitable solvents.[3] The oil has a high content of phosphatides, lecithin, and cephalin.[2] When cooled, liquefied fats containing lecithin solidify into a homogeneous mass, making oleomargarine and leather softeners.[2] The oil is second only to cottonseed oil as a lard substitute and vegetable shortening. Mixed with linseed oil to the proportion of 20 per cent, it is used in the manufacture of paints.[3] Its use was second only to cocoanut and cottonseed oil in the manufacture of soaps, and because of its high glycerin content, it is used in the manufacture of explosives. Other uses are for enamels, lacquers, linoleum, oil cloth, artificial leather, printer's inks, lubrication, and salad oils.[3]

The meal is eaten in breakfast foods, infants' foods, diabetic foods, and macaroni. The meal is ground up into flour and either used as pure soybean flour, or more often mixed with other flours. In the baking industry the following products may contain it: bread, rolls, cookies, cakes, sweet rolls, doughnuts, pie crust, crackers, muffins, and biscuits.[1] Used in the proportion of 3 to 5 per cent it retards the onset of staleness to these bakery products. Its addition lessens the breakage factor in crackers. Pound cakes are given a yellow color and retain their freshness longer on the addition of soybean flour. The meat packing industry uses soybean flour in making frankfurters, bologna, sausage, meat loaf, canned corn beef hash, and dog foods, for by adding it, the finely cut meat products are held firmly together.[1]

When the meal is soaked in water and boiled, a certain part of it goes into solution to form a soybean or vegetable milk.[3] As milk it is used

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in the making of bread, cakes, custards, and milk chocolate. In Japan a condensed variety is produced. This milk is fermented and various cheeses are made, the individual flavor varying with the ferment used. Nuso, Tofu, Hamananatto, Natto, and soy sauce, one of the ingredients of Worcestershire sauce, are fermented products.

The soybean protein contains a high percentage of glycerin, which chemically resembles milk casein.[2] When treated with formaldehyde, it is converted into a resin which is used in the sizing of paper, waterproof glue, and various plastics.[2] When great resistance to moisture and high dielectric strength are desired, the soybean protein is condensed with phenol and formaldehyde to form a synthetic resin.[2] These resins are used as a basis for varnish and lacquers, having great durability and a high gloss. They resist high temperatures well, are tough, and are water and alkali resistant. To the resins may be added cellulose, carbohydrates, or other fillers in the manufacture of molded plastic materials, such as dishes, panels, horn buttons on automobiles, and electric light switches.

Both the stalks and the meal are used for cattle fodder. Because of the high protein content, the meal is used as a fertilizer.

Duke[4] in 1934 reported five patients who were sensitive to soybean dust while working in a soybean mill. Olsen and Prickman[5] reported another case sensitive to the soybean dust. Piness[6] in discussing Duke's paper mentioned the importance of the soybean as a food, particularly in the diets of infants. An additional case of soybean sensitivity is here reported.

CASE REPORT

G. T., male, aged 33, had been suffering from asthma for two and a half years. His asthma was nonseasonal, fairly constant, having free periods of not more than a few days. He has had the fall type of hay fever for six years. He was treated with injections of ragweed extract in 1936 with partial relief from his hay fever, but not from his asthma. He works as a shipping clerk in a factory making rosins. For a time he noted he was worse while at work, improving when he came home at night.

Physical examination showed that he was a well built man of 35. His teeth had many decayed roots. His tonsils were removed, though he still had a remnant on the left. His heart was normal; blood pressure 110/80. His chest was of the barrel type. Breath sounds were distant and contained a few musical râles. X-rays of his teeth showed abscesses in three teeth on the upper jaw. X-rays of the sinus showed a veiling of the ethmoids and slight veiling of the antrum.

On skin testing he gave a marked reaction to dust, feathers, pea, lima bean, and soybean, and a moderate reaction to ragweed. To the soybean he gave a marked reaction in the strength of 0.001 mg. N per c.c. When this extract had been boiled for three minutes, his reaction remained the same. He was given a series of injections of dust and feather extracts, and also soybean extract, beginning with one protein unit. In ten months he had received up to 500 protein units of soybean extract. On the fourth injection of soybean he developed a moderate local reaction and within an hour had asthma. Passive transfer was accomplished with soybean, house dust, and lima bean.

He was hospitalized for a week and his teeth and sinuses were given attention. In the hospital he had no asthma, nor did he have asthma for another week when at home. When he returned to his work in the shipping room, he developed asthma within a day, requiring adrenalin for relief. When his job was changed from inside the plant to outside, working about the grounds, he remained free from asthma for five months.

On investigation of his working conditions it was found that he was shipping clerk in a factory making rosins. The place was of necessity dusty because of powdered rosin and hundreds of bags of wood flour. Adjoining the shipping room was a store room where 50 one-hundred-pound bags of soybean meal were found. The patient's asthma began at the time the meal arrived.

Because it was felt that he might be sensitive to only the dust of the soybean, as in Duke's reported cases, ingestion of the bean was attempted. After he had been free from asthma for a period of six months, he was given soybean by mouth in the form of "sobee." On three occasions after taking the sobee he developed asthma within three hours. He also developed asthma on eating peas, string beans, or lima beans.

SUMMARY

1. A case of asthma from soybean sensitivity is presented.

2. Sensitivity was found by direct skin test and by passive transfer.

3. Sensitivity occurred on inhalation and on ingestion.

4. Numerous uses of the soybean as a food and in industry are discussed.

5. Because of its widespread and increasing utilization, sensitivity to soybean should be constantly suspected.

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ASTHMA DUE TO SENSITIZATION TO A MUSHROOM FLY (APHIOCHAETA AGARICI)*†

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THE first case of asthma that has been found to be due to sensitization to a species of mushroom fly *(Aphiochaeta agarici)* is here reported, together with clinical and immunologic observations and the significant entomologic data.

CASE REPORT

W. B., a physician, aged 62, was first seen on April 28, 1936, with a chief complaint of asthma every spring and fall. The first asthmatic symptoms had appeared on March 23, 1933, apparently on the heels of an attack of grippe and bronchitis, and persisted through the month of April and into early May, with trouble each day and night. He then became symptom free until October 15, 1933, when asthma returned and continued until the end of November. In 1934, asthma was present from April 1 to about May 20, and again from October 15 to about the end of November. In 1935, the spring attack lasted from March 23 to early June, and the fall attack from October 10 to Thanksgiving. Symptoms in 1936 had begun on March 27. Spring attacks have lasted longer and have been more severe than those in the fall. Only the spring attacks of 1933 and 1935 had apparently been initiated by an infection with consequent purulent nasal discharge and sputum. In the others there were definite signs of nasal irritation, with sneezing, considerable watery nasal discharge, and also some itching of the eyes and lacrimation. The nasal and ocular symptoms in the spring and fall, and also a tendency to sneeze rather often at all seasons, had been noticed for two or three years before the onset of asthma. In recent years he has had several attacks of hives, and from time to time throughout his life he has had migraine. A brother suffers from allergic rhinitis.

The positive findings on physical examination included the usual typical pulmonary signs of active asthma, a markedly deflected nasal septum and hyperplastic changes in the nasal mucosa, with numerous small polypoid masses in the right ethmoidal area.

Extensive skin tests yielded a few weak to moderate food reactions, a moderate reaction to his own house dust, a questionable reaction to feathers and negative reactions to all other things tested, including 30 pollens.

In answer to the question as to whether anything in his environment seemed to have a relation to his asthma, he rather deprecatingly said that both he and his daughter had wondered why his trouble seemed to be present at the time when mushroom flies were numerous. On further questioning it developed that there was a close parallelism between both the time and the degree of prevalence of the flies in his neighborhood. Moreover the flies invaded his house in large numbers so that he assured me he could bring me a goodly quantity of the dead flies when the flies returned in the fall.

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†Read before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 30, 1938.

There proved to be a very small number of flies in the fall of 1936, and the patient had almost no asthma. In April, 1937, the fly crop was very large, and with it the patient again developed severe asthma. This time he was able to supply me with a goodly quantity of the flies.

The flies were extracted for forty-eight hours with Coca's solution, and the extract was sterilized by Berkefeld filtration. The resultant extract was found to have a nitrogen content of 0.33 mg. per cubic centimeter.

A skin test made in our patient by the intracutaneous injection of 0.02 c.c. of this extract gave a violent local reaction: an irregular wheal 25 mm. across and a surrounding zone of erythema, measuring about 80 mm. At the same time he experienced a mild constitutional reaction with wheezing. The same test in three control subjects was clearly negative. The patient was found to give positive skin tests to the extract in successive dilutions down to and including 0.00001 mg. N per cubic centimeter.

Normal skin sites were injected with the patient's serum and forty-eight hours later were tested with the fly extract. Strongly positive reactions were obtained with suitable negative controls, demonstrating the presence of a specific reagin in the patient's blood.

Treatment was begun in May, 1937, with 0.1 c.c. of an extract containing 0.000001 mg. N. The dosage had been carried up to 0.6 c.c. of an 0.01 extract by October. For the first time he went through the fall season without symptoms. During the following winter the dosage was carried up to 1 c.c. of 0.1 mg. N. In late March and April of this year there was an unusually heavy crop of flies, but he remained comfortable until April 19; for the next five days he had mild asthma at night and some sneezing by day. During the past week he has again been free of symptoms and he thinks the flies are becoming less numerous. (June 1, 1938: No further symptoms in a season with many flies.)

ENTOMOLOGIC DATA[1-3]

Mushroom culture is the most important single industry of the rural districts of Chester County, Pennsylvania, in which the patient lives, practically every farm having its group of mushroom houses. From 75 to 80 per cent of the mushrooms eaten in the United States are grown in the southeastern corner of Pennsylvania.

Mushroom flies are the most widespread and most destructive insect enemies of the cultivated mushroom. The damage is not caused by the flies, but by their larvae which feed in the manure of the mushroom beds, on the mycelium, and inside the stem and cap of the growing mushroom. There are several species of flies and gnats which are collectively known as mushroom flies, but by far the most numerous is a species of manure fly, *Aphiochaeta agarici*, of the family *Phoridae*.

The only medium for mushroom growing is a compost of horse manure. Manure piles 4 feet deep and covering areas of many square yards are prepared in connection with each mushroom house each spring and fall. At seven- to ten-day intervals, the compost is turned over as decomposition and fermentative changes take place. After five to seven weeks of such treatment, the compost is ready for use in the mushroom houses. It is during these periods of preparation of a compost in the first warm days of spring and again in the fall when the beds

are to be prepared for the winter that the *Aphiochaeta agarici* occurs in enormous numbers about the manure piles. With bodies measuring a little over a millimeter in length, these extremely active little flies swarm over the countryside. Not only can they get through ordinary fly screens, but they can even enter into the houses around the cracks and edges of closed windows and doors. In the mushroom houses fumigation with calcium cyanide or with nicotine is fairly effective. In dwelling houses apparently only pyrethrum is of any use.

The significant points as regards the possible role which these flies might be found to play as excitants of allergic phenomena are: (1) The enormous numbers in which the insects abound. (2) Their occurrence in two distinct seasons, in the early spring and late fall, depending upon weather conditions and the state of the compost piles. (3) The intensity of mushroom culture in any given neighborhood.

SUMMARY

1. There is reported the first case of asthma that has been found due to sensitization to a species of mushroom fly, *Aphiochaeta agarici.*

2. Symptoms occurred in the early spring and late fall at periods when the fly is plentiful.

3. An extract of these flies not only gave positive skin tests but was efficacious in treatment.

4. Specific reagin in the patient's serum was demonstrated by passive transfer technique.

5. The significant entomologic data are presented.

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BEET POLLEN AND BEET SEED DUST CAUSING HAY FEVER AND ASTHMA

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DURING the late spring, summer, and fall of 1936 a new important factor in the etiology of hay fever and asthma appeared in the Mesilla Valley of New Mexico and Texas. This Valley is the irrigated area along the Rio Grande river containing a number of small towns and villages with El Paso as its approximate center. For several years small patches of sugar beets have been experimented with as a new crop for the district. It was found that due to the long growing season and the mild winters, a seed crop could be produced each year in contrast to the usual two years required in most of the United States. As a result, a large acreage of the crop was planted, and with the late spring of 1936 beet pollen was thrown into the air in quantity for the first time.

The nearest fields to the city of El Paso are about ten miles distant and only occasional pollen granules are to be found on slides exposed in the city. The plant was found to be of importance in regard to hay fever only after a number of patients, who had had various periods of freedom from symptoms, began to complain of violent attacks of hay fever when motoring in the valley. After exposure of slides in the regions complained of, the pollen was found in large numbers and I became conscious of the radical change in the local crops.

My experience with the situation may be illustrated with a few brief case reports.

CASE REPORTS

Case 1.—Mrs. C. had been under treatment for three years with complete freedom from hay fever. Her home was in El Paso, but during the month of June, 1936, she moved to her summer home in the valley. Immediately, she began to have violent hay fever. In an effort to locate the cause she was given slides to expose at her new location. When they were examined, it was found that there were numerous granules identified as sugar beet pollen. Coseasonal treatment was attempted, but after a week her symptoms were so severe that she was advised to return to El Paso. Within two or three days all symptoms had subsided. Skin tests were markedly positive by the scratch method.

Case 2.—Mrs. H. had been under satisfactory treatment for two years. Her home was in the valley near large tracts of sugar beets. In June, 1936, she began to have violent symptoms and retesting showed no change in her pollen sensitivity, except that there was a marked reaction to sugar beet pollen, to which she had not been previously tested. Coseasonal treatment was instituted with some gradual improvement, but her symptoms persisted until the beet crop was harvested. After that she was comfortable for the rest of the season.

CASE 3.—Mr. J. had been under treatment for two years with excellent results. He lived in El Paso, but his work carried him daily into the valley. In June, 1936, he began to experience hay fever when in proximity to beet fields, but was free upon return to the city. Retesting to pollens showed the same results as in Case 2. Coseasonal treatment was only moderately successful, but after the beet crop was harvested he became much better and finished the season free from symptoms.

CASE 4.—L. C., a child, had perennial hay fever and slight asthma at times. Removal of excessive amounts of eggs from the diet and cats from the home had resulted in complete control of symptoms. In late May, 1936, she began to have violent hay fever and asthma of rather more severity than previously. Recheck of pollen tests gave a strong reaction to sugar beet pollen. Coseasonal treatment with very minute doses of extract was rapidly successful. Treatment was discontinued after the harvest.

The above cases illustrate the experience with a number of patients. During the summer and fall several new patients were seen who gave the history of having had hay fever for the first time during the 1936 beet season. Others who had had fall hay fever for many years had experienced late spring symptoms for the first time in 1936. Most of the cases giving this history were found to be markedly sensitive to beet pollen.

Because of the explosive violence of the symptoms which many patients experienced (those seen later in the season who presented marked skin reactions to the pollen), the probability of an increased pollen crop for the next few years, and the exaggerated difficulty of coseasonal treatment, it is to be predicted that beet pollen sensitivity will become one of our major problems in inhalant allergy in this locality.

Because of the interest of several patients who lived near beet fields, I had the opportunity to observe another interesting allergic phase of this new crop. As the plants were allowed to seed and require threshing, many of the local farm workers began to complain of a marked skin eruption that had the appearance of a contact dermatitis. I did not treat any of these cases but inspected several, and on inquiry elicited the fact that the condition was quite common. The threshing of the seed is, of necessity, a very dusty procedure, and as the clothes became saturated with the dust, the eruption appeared all over the body. Doubtless the dermatologists are familiar with this condition.

It was thought that the beet problem had been disposed of for the season, but in September the patient cited in Case 4 returned with hay fever and asthma. The mother inquired if the dust from the beet seed factory might be the cause. Investigation disclosed that the only plant yet in operation in the valley for the cleaning and sorting of the seed crop was located within several hundred yards of the patient's home. The dust incident to this cleaning process is enormous, and the surrounding community for some distance was covered with it. Samples were obtained and examined. It was found to be very light and buoyant,

almost free from pollen and composed of plant detritus. Extracts were made of it, and the patient reacted with definite skin tests. Treatment was begun with this extract, and within two weeks the patient was almost free from symptoms. It was subsequently learned that many other known allergic patients who lived within the range of the dust experienced symptoms when the large dust clouds were blown in from the plant.

Thus it seems that there has been introduced into this community a new agricultural industry that is most likely to become a serious factor to hay fever and asthma sufferers as well as to be a common eczema excitant to those who come in close contact with the plant.

The experience of 1936 was repeated in 1937. We now have about 100 patients who not only have given positive skin tests, but who have clinical symptoms when exposed to the pollen.

The plant is *Beta vulgaris* of the *Chenopodiaceae*. It pollinates from about the first of May until the middle of June. My impression is that the antigenicity of the pollen is maximal and that treatment is less successful than for the other pollens of this region.

SENSITIZATION TO JUTE*

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JUTE is a fiber obtained from one of two species of plants, either *Corchorus capsularis* or *Corchorus olitorius*. Both are grown in India in the province of Bengal north of Calcutta, a region from which nearly all of the commercial fiber is obtained. When the plants are mature, the tops and roots are cut from the stems and the stems are retted in pools of stagnant water until the fiber can be stripped free from the bark and woody parts of the stem. After the fiber has been cleaned, some of it is baled for export and the rest is woven into burlap and fashioned into bags. These bags are universally used for the transportation of coarse grains and agricultural products. Burlap, the coarsely woxen textile made from the fiber, is used for the protection of furniture and innumerable other articles in transportation. Some of the burlap and webbing made from jute enters into the construction of the less expensive upholstered furniture. Because of cheapness, jute is apparently supplanting more durable fibers used in weaving domestic rugs and carpets.

Several years ago a number of patients were found specifically sensitive to jute. Once attention was directed to this fiber as a possible allergen and its ubiquitous use realized, a careful study of its allergenic properties was undertaken. In the course of this research the reactions with dust extracts and with the extracts and proteins of jute fiber freshly exported from India were compared in patients who had asthma and hay fever. The two series of reactions almost paralleled. But it could not be concluded that jute was always the hypothetical "unknown" allergen contained in dust because jute extracts and the proteins precipitated from these extracts often caused immediate reactions seemingly of the purely irritative type. These reactions have been similar to the irritative reactions frequently encountered when testing with dust. Thus far no conclusion has been reached regarding these apparently spurious reactions. They may be intrinsic in the jute protein or they may be acquired as a result of retting. Although this phase of the problem has not been satisfactorily completed, the study has shown that jute is an allergen of some importance in asthma, rhinitis, and hay fever. The following case histories are reported merely to establish the allergenic properties of jute fiber preliminary to a more complete report, because no references to jute sensitization have so far been found in the literature.

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CASE REPORTS

CASE 1.—This patient was a choir singer who sang in stalls directly in front of playing organ pipes encased in decorative wood filigree backed with silk over burlap. Whenever she was in the stalls and the organ was played, she would cough. This cough increased in intensity, from a simple laryngeal irritation to actual asthmatic attacks, occurring only when she sang in church. Intracutaneous tests to extracts of jute fiber were positive, and her serum transferred the reaction to the skin of normal people. When she was exposed to fresh jute fiber artificially aged by mechanical pounding or to old fragile burlap, the symptoms were reproduced. She was successfully desensitized to jute so that her singing was not permanently interrupted. She ceased singing in the choir and discontinued the inoculations. Later, when playing in a stage part in which she was wrapped in burlap, mild symptoms recurred.

CASE 2.—This patient worked in the accounting office of an importing company. The office was at the warehouse entrance through which coffee in burlap bags was carried from the docks. When coffee was unloaded and housed, he had attacks of asthma. Attacks occurred also when he stayed in the warehouse for any time. Intracutaneous tests to coffee were negative but jute gave a positive reaction, which was passively transferable. Exposure to burlap and to powdered jute fiber caused asthma. Desensitization with protein precipitated from jute extracts relieved him of his asthma for over a year after inoculations were discontinued.

CASE 3.—Over a period of years an upholsterer developed a rhinitis which was ordinarily mild but became increasingly more acute whenever he entered the workroom of his shop. At times, especially when he assisted in unpacking crated furniture covered with burlap, the attacks were exceedingly severe and were accompanied by laryngitis and tracheitis. He showed a number of positive reactions when he was tested intracutaneously. The most strongly positive tests were obtained with feathers, cottonseed, kapok, jute, and pyrethrum; of these the reactions to feathers and jute could be transferred passively. He was tested by exposure to the substances giving the positive intracutaneous tests and reacted clinically only to cottonseed and to powdered jute fiber. Following inoculations with cotton extracts and extracts of jute, he could work in his shop comfortably with only occasional severe exacerbations of rhinitis, which occurred in a variety of environments. The cause of these exacerbations has not been determined with certainty, but they may be provoked by certain perfumes.

CASE 4.—A young man, 18 years of age, gradually acquired an almost continuous asthma. The asthma had begun with a cold in the fall of the year when he began work in a paper and printing factory. At first these attacks occurred only with colds, but he subsequently developed mild continuous asthma which lasted into the summer and ceased when he left work for several weeks. He was free from asthma during this interval, but on his return to work in the fall the asthma recurred with increased severity. He observed that even though free from asthma an attack started as soon as he began work in the morning and increased in severity as the day passed. Toward evening several ephedrine capsules were required to control the attacks. He found he seldom had attacks on Sunday and on holidays, and so definitely associated his asthma with his occupation. He worked at a baling machine. Paper scrap was brought to him from all parts of the mill in large burlap bags which he emptied. He showed numerous positive reactions to intracutaneous tests with extracts of inhalants but none which could be associated with his work, except jute and dust. He was exposed to powders made from dried inks used in the factory and to extracts of the paper scrap without having attacks. Intratracheal sprays of jute extracts and extracts of the burlap sacking used in the factory,

however, induced bronchospasm. Attempted desensitization resulted in frequent constitutional reactions with jute in low doses, so he was advised not to return to his former job. He subsequently had asthmatic attacks only after colds.

CASE 5.—A patient had both rhinitis and asthma, especially when dusting and cleaning house. She had had asthma in her youth but was comparatively well after leaving home to work in the city where she lived in a small apartment furnished with pieces of simple furniture she had brought to the city from her "dust free" room at home. During her period in the city she revisited home several times and had some asthma each time. The asthma on these occasions was attributed to contact with animals, to colds, or to climatic changes. She married and moved to a larger apartment which was furnished in part by her relatives. One piece of furniture, a long davenport, which was the only heavily upholstered piece of furniture in the new apartment, was brought from her childhood home. After several weeks in this apartment, she had rhinitis frequently while cleaning. On two occasions when sleeping on the davenport she had asthma. This davenport had box springs covered above and below with several layers of burlap and an outer covering of cotton material. Square leather cushions which covered the springs and the back of the davenport were filled with old horse hair and a layer of burlap next to the leather. In numerous places the leather had cracked and dust containing pieces of burlap and hair sifted through the holes. The only positive reactions obtained with 20 inhalants and approximately 60 foods were with dust and jute extracts. Subsequently her nasopharynx was sprayed with a strong extract of jute fiber during forced inhalation. This caused a severe attack of asthma. After the davenport was removed from her apartment, both the asthma and rhinitis ceased.

SUMMARY

Jute, a vegetable fiber grown in India, is widely used in the form of burlap for packing and transporting articles of merchandise. Because it is cheap, it is used also in place of more expensive and durable fibers in inexpensive upholstered furniture and in the cheaper domestic rugs and carpets. Inasmuch as it is used so ubiquitously, contact with jute is almost universal. Five case histories are given demonstrating conclusively the allergenic properties of jute.

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS*

THE Society for the Study of Asthma and Allied Conditions, in the comparatively short period of its existence, has a long series of splendid accomplishments to its credit. A glance at its membership roster reveals the names of practically all who have done the pioneering in the field of allergy. Its scientific programs include notable contributions both in the fundamental and in the clinical phases of hypersensitiveness. In such a record any organization may well find cause for satisfaction and impetus for further efforts.

Along what lines, you may ask, can we as a group contribute to the further development of allergy? I shall try to answer this question very briefly.

Both allergy societies have made a good beginning in the past few years by establishing an active joint Committee on Clinic Standards. As a result of the work of this Committee, allergy clinics throughout the country have had to improve their personnel and equipment in order to meet minimum requirements and obtain recognition. With recognition and frequent supervision, there followed a rise in professional standing, more research work and better service to patients, so that the clinics have grown to a point where they command the respect of the institutions which at first but tolerated them as a questionable experiment. Today the approved allergy clinic of any hospital compares very favorably with other special clinics in the same institution.

The practice of medicine is essentially individualistic. It is precisely this distinctiveness and independence of thought and critical variety of opinion which are responsible to a large extent for medical progress. There comes a time, however, in the growth of any science, when multiplicity of terminology and methods become confusing and retard advancement. Here again, it is felt by many, is an opportunity for us to assume a position of leadership. For there is no doubt that there is need for classification in the matter of methods and terminology. By pooling the combined experience of a group such as this some effort should be made by this Society in conjunction with the Association for the Study of Allergy at standardizing nomenclature, methods of preparation of extracts, methods of testing, and dosage in treatment. We

*Presidential address read by Dr. Leo H. Criep, Pittsburgh, Pa., before the Sixteenth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 30, 1938.

could well take a leaf out of the book of the American Heart Association which has formulated the classification of diseases of the heart, standardized digitalis therapy, and defined methods in electrocardiography—all of which have been approved and adopted by all competent cardiologists and cardiac clinics in the country.

The trend towards specialization in medicine has led to many efforts on the part of the profession to prevent the entrance of unworthy and unprepared men into these fields. Our Society can join in this effort by exercising great care in the admission of new members. Minimum professional qualifications should be established, such as years of practice in the specialty, publications, clinic affiliations, as well as personal integrity and reputation. The public, as well as the profession, is beginning to learn that membership in a recognized specialistic society is of itself presumptive proof of competence, hence an increased responsibility is involved in the choice of new members. In this connection, we should seriously consider joining the American Board of Medical Specialties and formulate some means for the certification of allergists. This should not be difficult. Those who already hold a Board certificate, say in internal medicine, in nose and throat, or in pediatrics, could be further certified in allergy, either on the basis of competitive examination or its equivalent—that is, membership in this Society, publications, teaching position, and the like. Others could qualify either on the basis of undisputed eminence and competence in this field or after proper examination. Our situation is, of course, no different than that which holds for the gastroenterologist or the cardiologist who is qualified as such after he has secured his certificate in internal medicine.

The public has received a liberal education in allergy as a result of much that has appeared in the newspapers and lay magazines. This growth of public interest often brings the allergic patient to his physician who not infrequently, because of a lack of proper understanding of the subject, fails to give his patient adequate allergic care. Further steps should be taken, therefore, to stimulate undergraduate and graduate education in this field. Much has already been done, but more can be accomplished. A joint committee should be appointed whose duty it shall be to further interest the Council on Medical Education of the American Medical Association and the curriculum committees of the medical schools in the country in the establishment of a standardized course in allergy. This should include a discussion of anaphylaxis and related phenomena as part of the course in immunology; a discussion of the pathology of allergy in the course in general pathology, and about six to eight hours devoted to didactic lectures in clinical allergy as part of the course in medicine. Provisions should also be made for clinical clerking and dispensary work in allergy during the senior year.

Graduate education is accomplished through hospital staff conferences and county and state medical society meetings. Through this medium,

the practicing physician must receive an intelligent and conservative view of the scope of usefulness as well as limitations of allergic diagnosis and treatment. He must be given to understand that such diagnosis consists of careful clinical investigation and not in the mere mechanical performance of certain tests.

Our own meetings can continue to provide further light and stimulation. There are few fields in medicine that afford a wider opportunity for original investigation and clinical observation. The surface has barely been scratched. And perhaps because of the very newness of allergy, involving as it does a certain amount of skepticism on the part of the general profession, we must be ever watchful and guard against unfounded conclusions and wild claims. These meetings should, therefore, serve as a clearing house where scientific propositions, regardless of source, can be carefully and critically scrutinized, upheld if tenable and frankly condemned if otherwise.

Allergy is here to stay in the family of medical specialties. Its rapid progress is attested to by the successful growth of allergy clinics throughout the country, the voluminous and worthwhile literature on the subject, the appearance of the JOURNAL OF ALLERGY, numerous commendable books written all by members of this organization, the inclusion of chapters on allergy in textbooks on medicine, and the ever increasing tendency for medical schools to adopt its teaching in the curriculum. In this rapid advancement this Society and its members have played and can continue to play an important role.

Annual Review

ALLERGIC DISEASES IN CHILDHOOD*

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THE problems presented by allergy in childhood have continued to attract the attention of pediatricians and allergists both in this country and abroad. Investigation has been along many different lines. One interesting study is that which has been going on at the Associated Foundation at Western Reserve University. T. Wingate Todd and his co-workers[1-4] have recently described changes in the growing ends of long bones which were attributed to mild gastro-intestinal upsets. The changes consisted in fine transverse lines of increased density in the ends of the shafts of long bones. These lines were wavy and gave a watered silk appearance. They were called scorings, in contrast with scars which were more dense and wider. Scorings did not extend across the entire width of the bone while scars did; they disappeared after a few years and they were noticed especially in allergic cases. In order to evaluate the part that allergy played in producing the "scorings," the results of 805 detailed examinations of children from 2½ to 16 years were analyzed statistically. Seventy-six per cent were found to present definite clinical signs of allergy and 60 per cent of these showed scorings. In the group without evidence of allergy, 37 per cent showed scorings. This is a significant difference and indicates an association between allergy and scorings. Seventy-six per cent, however, seems a surprisingly high percentage of children to show definite clinical allergy from a group of 805 who were unselected, save that they tended to come from better class Cleveland homes.

Carrying the inquiry further Cohen and Friedmar[2] found scorings in practically every allergic child they investigated with food allergy, whereas they were seldom present in those with pure inhalant allergy. Inasmuch as over a third of supposedly nonallergic children had shown scorings in the previous study, this appears to be an inconsistency. Nevertheless, Cohen was able to use the presence or absence of scorings as an index of the presence or absence of food allergy. He feels the significance of positive food tests can be settled in this way and that the roentgenogram can be used as a guide in trial diets. So long as new scorings continue to appear, food allergy is assumed to be active.

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Shortly before Cohen's report was published, Chobot and Merrill[5] reported the study of 30 infants and children for bone scoring. Seventeen of the group were allergic, but no differentiation was made between food and inhalant allergy. The majority of both the control and allergic groups showed transverse lines which were described as "scorings." One gets the impression from this article, however, that possibly no distinction was made between "scars" and "scorings," and unfortunately the reproductions of the roentgenograms do not lend themselves to this differentiation either. Nevertheless, it is significant that growth disturbance lines of some type were found in 14 out of 16 control cases. It seems to the reviewer that one very likely explanation of Chobot's figures is that he dealt with clinic children in an overcrowded city (New York) where one might reasonably expect to find numerous factors of growth disturbance, quite apart from allergy.

In what is apparently a reply to Chobot and Merrill's article, Todd has explained his views further in a letter to the editor of this journal.[6] In it he states that neither he nor Cohen has claimed scorings to be pathognomonic of allergy, but simply indicative of gastrointestinal disturbance. If the disturbance is allergic in origin, the scorings can be used as an indication of progress of the allergy somewhat as the temperature record can be used as an index of progress in pneumonia.

Elsewhere Todd[7] enumerates other findings frequently seen in allergic children. These include a high palate, poorly developed facial skeleton, and a restricted dental arch. If adenoid obstruction is present, it is probably edematous in nature and subject to fluctuations with the condition of the nose and sinuses. If removed, it tends to recur. These fluctuations of the adenoid can be shown by roentgenogram if a specialized technique, devised by Broadbent, is used. Similarly, thickening of the turbinates can be shown roentgenographically as can the associated failure of proper growth of the face in the nasal areas. The allergic facies, incorrectly called the adenoid facies, is the result of this failure of proper growth.

Mineralization of bone is light during the active phase of gastrointestinal allergy and administration of mineral will not correct this, according to Todd. Furthermore, the tissues become water-logged, he states, and clear distinction between skin, subcutaneous tissue and muscle by roentgenograms, normally possible, is lost. When the allergy causing the hydration clears, the water is lost and weight drops.

These statements are sweeping in nature, and if confirmed, reveal an interesting and new field of study. Unfortunately, the roentgenographic technique involved in reliable demonstration of degrees of mineralization and tissue density is such that at the present time few are prepared to undertake it. A different approach, such as that of mineral or water balance studies, might prove equally difficult. On

the other hand, scorings are more easily studied. Todd's prediction[8] that they can be used as warnings that gastrointestinal allergy is quite probable even though not apparent, merits further careful work on this subject. However, since they are not specific for allergy, ruling out other causes would always seem to present a problem.

ACQUISITION AND PROPHYLAXIS

Ratner has long championed the close relationship between allergy and anaphylaxis. In an article[9] discussing the modes of acquisition of allergy, he naturally turns to the evidence in the experimental acquisition of anaphylaxis in animals. These involve intrauterine sensitization, ingestion, inhalation, and injection; that is, the crossing of the placental, intestinal, respiratory, or skin barriers by unaltered protein. He points out that intrauterine sensitization in this way may lead to a congenital allergy which, in the absence of evidence of the first contact, can give the appearance of allergy due to constitutional factors. It seems to the reviewer that both viewpoints are not mutually exclusive. The allergy could depend on the type of intrauterine sensitization Ratner describes and in addition upon the constitutional capacity of the fetus to become sensitized. Although Ratner admits that no evidence is presented concerning the inheritance or constitutional factors, he goes on to make a comparison of their relative importance with factors of exposure in producing allergic disease in the human being, and concludes the latter is of greater importance. Such a deduction would not seem justified on the evidence he presents. Ratner apparently does not deny the presence of a constitutional factor, but believes it present in everyone, the question apparently being to what extent.

In another article[10] Ratner expresses his views on the prophylaxis of allergy. This, too, is built around the anaphylactic "first contact" theory. To prevent intrauterine sensitization he proposes that the pregnant woman limit her protein intake, not indulge food cravings, and limit the amount of food in certain groups, such as nuts and fish; also, that proteins which she eats be altered by heat where possible, as in the case of eggs and milk.

The same food precautions, he says, should be followed in early childhood and during illness and convalescence, periods of mucous membrane permeability. In infancy cow's milk should be denatured by heat, too early introduction of new foods in the infant's diet should be discouraged, and overeating of seasonal foods should be avoided. House dust sensitivity and bacterial allergy are to be prevented by avoiding house dust inhalation in the nursery and respiratory infection. Ratner inclines to attribute much of the common cold to bacterial allergy. His views were further expressed in a roundtable discussion.[11]

The program outlined above involves constant attention over a period of years by both obstetrician and pediatrician to many factors at present not receiving particular notice. Until a large enough group of mothers and infants are thus carefully supervised, the effectiveness of such a program will remain undemonstrated. The theoretical grounds upon which it is based are, moreover, still insufficiently explored. The reader is referred to Walzer's[12] excellent discussion of these grounds in his recent critical review.

PASSIVE TRANSFER STUDIES

Lippard and Schmidt[13] have done some interesting work with human passive transfer antibody. In studying the properties of the latter they realized that some method of titrating it was necessary and that the end points obtained when progressive dilutions of serum were used were not clear cut. Instead they used a mixture of 0.4 c.c. of serum with progressive dilutions of antigen. These mixtures were used in preparing passive transfer sites in normal recipients. One to three days later, 3 c.c. of a concentrated extract of the antigen were injected intramuscularly at a distant site. The previously sensitized sites were observed for wheals. The titer of the serum was based on the antigen concentration of the mixture which just failed to give a reaction, that is, where sensitization had been inhibited. End points by this method were comparatively sharp and constant in different recipients. Among the antigens used were peanut, egg, codfish, horse dander, silk, ragweed, and grass. One general reaction in the form of urticaria and asthma occurred from the injection of peanut antigen. The danger of acquired sensitivity, the pathway being one of those listed above by Ratner, was apparently not great. One hundred and seven recipients were tested intradermally at frequent intervals for three months after the intramuscular injection of antigen, and only 6 showed small and transient increases in their cutaneous reactions and none showed clinical sensitivity. Many of our therapeutic measures, of course, involve similar injections of protein. An exact counterpart is the injection of sterile milk for nonspecific protein shock. It is interesting to note that storage for six months did not alter the results obtained with the antigen-antibody mixture and that sites injected with the mixture were still active, even though they were not used for forty-five days.

In a later article[14] the same authors report on the neutralization of antigen rather than of antibody. They were interested in how completely the presence of passive transfer antibody neutralized or inhibited the antigen in a mixture of the two. Mixtures containing an excess of antibody as shown by the above titration method were used. The mixtures were injected into naturally and artificially sensitized skins. No reaction was obtained in 12 out of 13 trials, showing that

the antigen had been completely "bound" by the antibody. The absence of such neutralization had been offered as evidence of the difference between anaphylaxis and allergy. Harley[15] has also demonstrated the neutralization of pollen antigen by specific serum.

The probability that two antibodies, a sensitizing one and an inhibiting one, were concerned in the above experiments is indicated by the author's statement that heat up to 56° C. caused a loss of the sensitizing power of the serum, but did not destroy its ability to neutralize specific antibody. That at least two such independent antibodies are often present was indicated in an earlier observation of Cooke[16] and his co-workers. They had observed a greater neutralizing ability without change in sensitizing capacity in the serum of ragweed sensitive patients after treatment. More recently Cooke, Loveless, and Stull[17] have separated the two antibodies by demonstrating the production of an inhibiting antibody in normal individuals who have been "treated" with ragweed antigen. The same individuals developed no sensitizing antibody at all. The antibody produced in sheep immunized with ragweed extract and described by Cohen and Nelson[18] seems to be related to that discussed by Cooke, Loveless, and Stull.

PSYCHOLOGIC FACTORS

Recent studies of the psychologic factors in the allergic child have been reported chiefly from England. Rogerson[19] has made a detailed study of 30 unselected cases of asthma and eczema at Guys Hospital where Strauss[20] has studied adult asthmatics from the same standpoint. He finds an asthma-eczema personality in which a high intelligence and underlying aggressiveness are combined with overanxiety and insecurity. Besides this personality-likeness an environment-likeness is apt to be present in overprotective and overanxious parents. For comparison he uses 30 nonasthmatic children taken from the same clinic group. These are not true controls as they were all referred for psychologic difficulties. Six of the latter group are described as restless, excitable, or overactive; six as overanxious or afraid, and four as bad tempered or aggressive. The corresponding figures from the asthma group are 19, 16, and 9. As evidence against the likelihood that these are all acquired rather than inborn characteristics, Rogerson cites an inborn quality: the high intelligence quotient. The average of 25 asthmatics tested by the Binet system was 108.8. In such a small group this does not strike the reviewer as a particularly significant deviation. Rogerson's comparison of the I.Q. average of 108.8 with the score of 89 made by 321 other children at the same clinic is not warranted, as the latter group were all referred as psychologic problems, and the test is based on a normal of 100. Feinberg[21] has already pointed out that to avoid the effect of sedentary occupation, usually of a mental form in coloring such tests, it might

be more logical to select a less handicapping allergy than asthma—hay fever for instance—in searching for constitutional differences in the allergic group.

In another British study Clarkson[22] also discusses the psychologic make-up and the nervous factors in the allergic child, whom he finds oversensitive and apprehensive, and with faulty hereditary inhibition of emotional stimulae. He feels that allergy enhances the pre-existing psychic disturbance and that besides clinical evidence of this there is biologic evidence as well. However, in illustration of biologic influence over psychic states he cites what is apparently an instance of the reverse. This is a case in which by hypnosis he caused a negative reaction on an intradermal test to egg in a girl who previously and subsequently gave a markedly positive test to egg. In certain instances, Clarkson feels, the psychologic phenomena in asthma are not primary but are "entirely dependent on disordered biochemistry." Just what the nature of the disordered biochemistry is, is not clear.

In the case discussions of these and other articles dealing with the psychologic aspects of asthma, the reviewer has felt that a more detailed account of what dietary, environmental, and therapeutic factors could also have been involved in the course taken by the disease might well be in order. An evaluation of the effects of the psychic approach on the problem is most difficult where all the details of the case from the allergist's as well as the psychiatrist's point of view are not available.

American authors who have recently emphasized the personality differences and difficulties of the allergic child are Todd[23] and Stokes.[24] Todd finds nervous tension, distractibility, restlessness, and short attention span, together with irritability, whining, and proneness to fatigue. Usually there is conflict with parents whose patience is none too great nor improved by the allergy they themselves may have. Contrary to Rogerson, Todd finds that the intelligence quotient is, if anything, apt to be temporarily lowered by an active allergic state.

Stokes describes the allergic child as one who is overactive, intensely excitable, and egocentric in his make-up. In the office they can be recognized "almost before being seen by their ceaseless activity, their precocious remarks, their noise and their desperately inquiring and investigative minds." Their rearing is an educational problem, and is often filled with conflicts with equally high-strung parents. The parent of the same sex, he says, often proves an invincible stumbling block in the rearing of such a child to nervous and mental calm and balance. The successful treatment of the allergic child, Stokes feels, must take into consideration adjustments of these factors as well as the more usual procedures.

LaMarr,[25] in his study of asthmatic children at New York Hospital, also feels that there is a clear-cut asthmatic personality type and that in treatment it deserves more recognition than has been accorded it.

ECZEMA

Turning to the field of eczema Hill[26] reports positive intracutaneous tests to feathers and house dust in over half of the cases of infantile eczema (atopic dermatitis) which he tested. These infants were consistently negative to both patch and scratch tests to the same antigens. This was in contrast then with the frequent positive patch test to feathers found by Peck and Salomon[27] in these children. Hill's control infants had negative tests, but the majority of adults used in passive transfer studies showed positive reactions at the unprepared control sites. Removal of dust and feathers had no noticeable effect on the infants with eczema. The question is raised whether the skin tests in atopic dermatitis can ever be used as a major guide in treatment and whether positive tests to allergens, such as house dust and feathers at least, are not normal for the adult. Further light on these questions is given in a later report by the same author.[28] Fifty-six per cent of a large group of infants with eczema gave a positive intracutaneous test to Lederle's cow's whey (1:1000). Of 19 of these who were placed on a milk-free diet, 74 per cent made a striking improvement. Goat's lactalbumin was used as a control in these studies and was positive in 15 per cent of cases. Normal infants gave a whey reaction in 10 per cent of cases. Scratch tests to milk were usually negative, but wheat, house dust, and feathers were apt to be positive intradermally in addition to milk. In a report to the Society for Pediatric Research, Lippard[29] defined even more clearly the exaggeration and intensification of immune responses which the allergic infant with eczema shows in comparison with the normal. Whereas in his study of normal infants a small percentage of the latter developed positive skin tests and complement fixation antibodies following ingestion of milk and eggs, a much larger percentage of the eczematous group did so. In the latter group complement fixation could be detected in much higher dilutions of serums, and the prozone phenomenon was frequently present (negative complement fixation test in lower dilutions and positive in higher dilutions). Moreover, passive transfer of the positive skin test was possible in several of the eczematous but none of the normal group. The duration of the positive test in terms of months was variable in both groups, but consistently longer in the babies with eczema. Furthermore, among the normal infants, Lippard found positive skin tests to egg only in those who had been fed raw egg and none among those who had had only cooked egg. Half of the eczema group who had been fed no egg at all had positive tests, and almost all who had eaten egg were positive. No attempt was made to evaluate these reactions from the standpoint of therapy. Lippard pointed out that the immune responses of eczema were largely an exaggeration of the normal.

Finkelstein[30] has studied eczema for a number of years and his views on the subject are interesting. Cutaneous tests are not used. He feels milk is definitely harmful and reduces its intake or eliminates it. Sodium chloride intake is also reduced, since there is a tendency to increased retention of water and salt in eczema which must be overcome. A fruit and vegetable carbohydrate diet, free from fat, is used to which is added vegetable protein. When improvement has occurred, small amounts of animal protein are added, such as buttermilk or cottage cheese. It might seem that such a program would depend for its effectiveness upon the factor of milk elimination as emphasized by Hill,[31] but Finklestein says milk elimination alone is usually not successful. He aptly compares the present dietetic management of eczema with the situation with diabetes before the insulin era. The "insulin" of eczema is yet to be found.

The treatment of eczema outlined by Schneider[32] of Cologne is based on the same principles as Finklestein has outlined. Schornstein[33] of Marburg, Germany, reports the effect of such a diet, poor in salt and fat and rich in plant protein and carbohydrate, on serum lipoids and iodine number in 9 normal children. The negative results of his study are not conclusive as the diet was given over a period of three or four days only. He had previously confirmed Hansen's work by finding an average iodine number of 118 in infants with eczema as compared with 150 in the controls. The total serum lipids of the two groups, which consisted of 25 infants each, did not differ.

Graves and Dowman[34] and also Naumann[35] have pointed out the predisposition of the eczematous infant to a hematogenous dissemination of the virus of vaccinia quite apart from the question of surface dissemination.

The most novel attempt at the treatment of eczema is that of Sprenkel,[36] who advocates injecting the mother with normal saline, Ringer's solution or distilled water. It is recommended only where the infant is breast fed.

BREAST-MILK STUDIES

Another startling report is that of Sterling and Fishman.[37] They investigated the case of paroxysmal sneezing in a five-week-old breast-fed infant whose mother had been treated with ragweed antigen during pregnancy. The breast milk was used for skin tests in five ragweed sensitive patients. Cow's milk was used as a control. On the basis of two slightly positive reactions, it is concluded that ragweed antigen was in the milk. The infant was not skin tested, but nevertheless the clinical story is accepted as evidence of its sensitivity.

A more acceptable study dealing with breast-milk immunology is that of Ludwig Schneider.[38] He studied the presence of agglutinins for different *B. coli* strains in the mother's blood and breast milk, and

in the cord and infant's blood, in five cases. In most instances the titer of the mother's breast milk was higher than her blood titer, but in no instance could breast feeding be shown to raise the level in the infant's blood. In fact, the latter (apparently dependent on passive ante-natal transmission), dropped to lower levels as time elapsed. These results on a small number of infants are contrary to those reported by Toomey.[39] The latter, also working with enteric bacilli agglutinins, concluded that placental transmission was slight and that breast milk raised the infant's titer greatly. He did not, however, prove the point by studying infants who were not put to breast. Schneider's work, although on fewer infants, seems better controlled.

OTHER INVESTIGATIONS

Stoesser and Cook[40] report on the treatment of intractable asthma in children with hypertonic intravenous dextrose solution. Its beneficial results, they believe, are due to a specific action of dextrose, and not its hypertonicity. Hypertonic sucrose, for example, aggravated the symptoms in some cases. It was effective in asthma due to ingestants but much less so with inhalants. Possibly of greater interest are the observations these authors have made on the role played by sodium chloride.[40, 41] The cases which did not respond to carbohydrate therapy appeared to be influenced by shifts in the sodium chloride intake in the diet. A low salt diet was associated with improvement and a high salt diet with aggravation of the asthma. Attempts were made to differentiate the electrolyte from the hydration effects. If pitressin was given in doses sufficient to increase weight while the patient was on a low salt diet, further improvement occurred. Potassium chloride administration did not have a consistent effect, but when its administration was stopped, consistent improvement or cessation of asthma occurred. There was no effect from artificial fever, unless it was preceded by a low salt diet. The exact interpretation of these findings is not possible at the present time, as Cook and Stoesser themselves remark. Operation of some of the factors concerned in epilepsy is, of course, suggested, and it is felt at the Minnesota school, where this investigation has taken place, that cell membrane permeability plays a major role in the latter disease.

From the same clinic Stoesser and Cutts[42] recently reported on the relative value of the diagnostic procedures in the allergic child. They suggest elimination diets and skin tests by pressure-puncture in eczema, intracutaneous test in allergic rhinitis, pressure-puncture tests in hay fever, puncture and intracutaneous tests in asthma, and elimination diets in urticaria and gastrointestinal allergy. While the article intended only to discuss diagnostic procedures of the types listed, one misses any mention of the all-important history and general detective work as diagnostic procedures in their own right.

The variety of alterations in tone and motility of the gastrointestinal tract associated with the presence of an offending allergen is shown in the report of Fries and Zizmor.[43] In a study of 12 children known to have gastrointestinal symptoms due to food allergy, they found a variety of effects, including gastric retention, increased or decreased motility of the gastrointestinal tract, and spasm or dilatation of the stomach or intestine. This report would indicate that smooth muscle spasm is not an invariable response in these cases. Such is the position taken by Walzer,[44] who contends that edema of the mucous membrane, not smooth muscle spasm, is the essential lesion of gastrointestinal allergy.

One of the limitations of such a study is that only changes in muscle tone in that portion of the intestinal tract visualized by barium are seen. Absorbed antigen could cause changes elsewhere in the tract and fail to be noted.

Other interesting studies have doubtless been reported in the field of children's allergy which have not come to the reviewer's attention, and a few omissions have been intentional. Only time will tell which of the enumerated contributions have been of permanent value.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Rhinitis Spastica Tropicalis (Tropical Hay Fever). Castellani, Aldo: J. Trop. Med. **41**: 98, 1938.

The writer states that hay fever and asthma are not at all rare in the tropics and subtropics, but unfortunately not much is known about the allergens of tropical countries. Rhinitis *spastica tropicalis* (tropical hay fever) presents the same symptoms and is clinically identical with the hay fever of the temperate zone, except that it is caused by different antigens.

The common hay fever-causing allergens mentioned are *Euphorbia candelabrum*, tall veldt grasses *(Eragrostis plana)*, creeping grasses *(Cynodon dactylon)*, the pepper tree *(Schinus molle)*, the cinnamon tree, scales and hairs of insects, copra dust, and tea dust; also materials handled by workers, such as spices, sugar cane, and reeds. Some observers believe that the symptoms produced by the five last named articles are not due to the materials per se, but to insects or fungi so often found parasitic upon them. The author mentions the observations of Ellis that at Port Soudan on the Red Sea, hay fever and asthma are common and are caused by large amounts of mold spores in the atmosphere.

On account of the poorly developed knowledge of the allergens responsible, the diagnosis is made mainly upon the character of the symptoms and the history, while treatment consists of symptomatic and palliative measures.

Bronchiectasis. A New Conception of Its Etiology Which Makes Prevention and Recovery Possible. Watson, Samuel H., and Kibler, Charles S.: J. A. M. A. **111**: 394, 1938.

The authors state that more than 90 per cent of the patients with bronchiectasis that they have studied are allergic on the basis of eosinophiles, skin tests, and associated allergic disease. They divide their cases into four types:

1. Cases with signs and symptoms of bronchiectasis but x-ray examination with iodized oil revealing no evidence of bronchial dilatation (basal allergic bronchitis).
2. Cases like the foregoing with slight bronchiectasis.
3. Cases in which there is moderate bronchiectasis.
4. Cases in which there is far-advanced bronchiectasis, with marked pocketing.

The conception is then advanced that following allergic basal bronchitis, local atelectasis occurs, and by virtue of surrounding compensation emphysema, pulling is produced on the bronchial branches, favoring pocketing, and consequently bronchiectasis.

Therefore, if this basal allergic bronchitis is recognized and is treated by allergic management, bronchiectasis will not occur. The early stages of bronchiectasis are still remediable with the same kind of management.

The authors select one case from their series to illustrate the results attained in each type under allergic management.

Six Hundred Asthma Histories. Brief Comments on Therapy and Results. Cruciani, J. A.: Semana méd. **1**: 173, 1938.

This paper is based on ten years of observation in the Ramos Mejia Hospital in Buenos Aires. Tuberculin treatment was employed in 178 cases, among which were some who were also treated with gold salts. This treatment resulted in improvement in about 65 per cent. About 13 per cent of the patients were regarded as syphilitic.

Treatment of Hay Fever and Ivy Poisoning by Local Desensitization With Sodium Oleate and Salts of Other Unsaturated Fatty Acids. Lazell, E. W.: M. Bull. Vet. Admin. **14**: 216, 1938.

Sodium oleate, a normal constituent of bile, has been used as a detoxifying agent of toxoids before being displaced by formalin. The author felt that it might be of value in "detoxifying" allergic tissue and therefore employed it in the following types of cases: (1) In allergic eczema from pollen, etc., in the form of 10 per cent aqueous wet dressings or 10 per cent lanolin ointment. (2) In ivy poisoning. A bath containing sodium oleate is made and the patient lies in it several times a day, one-half hour at a time. (3) In hay fever it is used in concentration of 1:10,000. It is employed in the eyes, or as a nasal spray. In all cases where these methods were used the symptoms disappeared in three to four days and did not recur the rest of the season.

Systematization of Therapy of Grave Asthma. Malamud, T.: Prensa méd. argent. **25**: 115, 1938.

The author contributes a medicinal formulary of positive therapeutic action in severe asthma essentially concerning the immediate treatment in the acute phase: calcium chloride, atropine intravenously; hyperthermic medication. The utilized hyperthermia-producing agents are peptone 4 per cent, intravenously; and sulfur in oily suspension, intramuscularly; occasionally, fixation abscess and intravenous antityphoid serum. Sulfur is accorded the preference; the treatment is applicable in all forms of asthma. In the majority of 19 reported cases of grave asthma, the effects of this therapy were encouraging.

Treatment of Ragweed Pollenosis. Comparison of Oral and Hypodermic Medication. Bohner, C. B.: J. Indiana M. A. **31**: 279, 1938.

Bohner treated during the 1937 season, which was a particularly severe one in Indianapolis, a mixed group of 21 ragweed hay fever patients with ether extracted ragweed pollen given orally and dispensed in capsules. Treatment was started preseasonally the initial dose being 500 Noon units taken at weekly intervals and ingradually increasing dosage until the thirteenth and maximum dose of 120,000 Noon units was reached. This quantity was continued weekly until the season ended. In this group, 4 obtained excellent results, 9 had good results, one had only a poor result, and complete failure occurred in 7 cases.

Another group of 21 patients who were treated by the usual hypodermic method, either perennially or preseasonally, gave the following result: excellent, 8; good, 8; poor, 4; and complete failure, 1. The cases treated orally showed many more complete failures, and 16 of 21 subcutaneously treated cases received either excellent or good results, as compared with 13 receiving the same degree of relief in the cases treated orally.

Two of the cases exhibited gastrointestinal symptoms upon taking the large 120,000 unit dose by mouth. Both of these patients were very sensitive and usually had systemic reactions upon injection of 400 to 500 units of ragweed extract.

Treatment of Hay Fever With Forapin. von der Trappen, P.: Therap. d. Gegen. **79**: 44, 1938.

Last year Haag and König reported very good results in the treatment of hay fever with intracutaneous injections of bee venom (Forapin). Wheals were made on the forearm beginning with a test injection after which concentrations A, B, and C were used consecutively, increasing up to 6 wheals with each. The injections were given every two to three days. Although the author started these injections on himself shortly before the hay fever season, the results were most astonishing. Usually the hay fever season was almost intolerable to him, whereas now he has no symptoms. There is no unpleasant effect beyond the reaction about the wheal. This reaction is usually most definite in the cases giving the best response to treatment.

At the Schittenhelm Clinic it has been shown that in rheumatic patients the cholesterin index of the blood is increased following injection of this bee venom. It is possible that the cholesterin binds the toxins in hay fever as it does bacterial toxins. Many writers have drawn attention to the relation between rheumatic and allergic diseases.

According to Lumière and other writers cholesterin does exert a protective action against anaphylactic shock. It is, therefore, suggested that bee venom be tried therapeutically also in bronchial asthma.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY, AND JOSEPH GOODMAN, BOSTON

Studies in Contact Dermatitis. III. Active Sensitization With Krameria in Man. Grolnick, M.: J. Invest. Dermat. **1**: 179, 1938.

Patch tests with fluidextract of Krameria performed on 100 individuals revealed mild reactions which appeared in seven patients within a week. One of these seven reactors developed a marked reaction and a spreading dermatitis by the fourteenth day after application of the patch test. An attempt was made to sensitize to Krameria 37 subjects who showed negative reactions to an initial test with Krameria. Sensitization was accomplished in 32 instances, in the majority of cases by one to three applications of the fluidextract, but in others only after four to eight applications. Five subjects were not sensitized by seven to ten applications. The incubation period of sensitization in the 10 subjects sensitized by a single application was ten to twenty-one days.

When several applications were made to a single patient, there was frequently a flare-up, after the sensitization was established, of the sites of previous applications of fluidextract of Krameria. Sensitivity, once established, was found to be present on the whole skin surface. Sensitivity to Krameria has been observed to be present seven months after artificial sensitization, and almost four years in a patient who was found to have an acute dermatitis from Krameria contained in a hemorrhoidal ointment.

Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs. I. Cutaneous and Anaphylactic Responses to Old Arsphenamine and Neoarsphenamine After Sensitization With Old Arsphenamine. Frei, W., and Sulzberger, M. B.: J. Invest. Dermat. **1**: 191, 1938.

The authors observed that guinea pigs, sensitized to old arsphenamine by intracutaneous injection, showed anaphylactic symptoms in only a few instances after the intracardiac reinjection of old arsphenamine plus homologous serum. However, when

such injections were made by the intravenous route, severe anaphylactic reactions were usual. On the other hand, guinea pigs similarly sensitized to old arsphenamine, in spite of showing strong skin reactions to neoarsphenamine, showed no anaphylactic symptoms after the intravenous injection of neoarsphenamine plus homologous serum. The authors conclude that under the conditions of their experiments "old arsphenamine regularly produces a cutaneous sensitivity to itself as well as to neoarsphenamine. . . . Moreover, intracutaneous injection of old arsphenamine generally produces anaphylactic sensitivity to old arsphenamine but not to the neoarsphenamines."

Experimental Arsphenamine Sensitization. Further Observations on the Reactions to Arsphenamine in Guinea Pigs Given Staphylococcus Toxin, and in Guinea Pigs With Induced Streptococcal Infections. Cormia, F. E.: J. Invest. Dermat. **1**: 199, 1938.

The experiments reported in this paper are concerned with the effect of injections of staphylococcus toxin and of experimentally induced streptococcus infections on the sensitization of guinea pigs to arsphenamine.

Injections of staphylococcus toxin had no effect on the sensitization to arsphenamine, even when the diet was low in vitamin C. However, infection of guinea pigs with group C hemolytic streptococci resulted in increased hypersensitivity of the skin as evidenced by the increased intensity of reactions to reinjections of arsphenamine. A diet high in vitamin C inhibited this effect.

Urticaria. VI. A New Immunologic Wheal Produced Experimentally by Reverse Technic. Walzer, A.: Arch. Dermat. & Syph. **38**: 1, 1938.

The author describes a new type of wheal of internal origin, produced by the ingestion of an antigen followed by local passive sensitization by means of the injection of a reaginic serum. The wheals produced by this procedure develop at the site of injection of the reaginic serum. They are relatively smaller than those produced by the usual procedure of first injecting the serum and then ingesting the antigen. These wheals are further characterized by a circumscribed edema or indurated nodule which is most pronounced three to five hours after the ingestion of the antigen and which, in some instances, lasts as long as fourteen hours.

The author summarizes the factors possibly responsible for the formation of this type of wheal as follows:

1. The presence of circulatory antigen before sensitization.
2. The slow and difficult fixation of the reagins.
3. A refractoriness of the superficial capillaries.
4. The involvement of the deeper vessels.
5. The progressive diminution of the amount of antigen in the blood.

The author also discusses the possible clinical importance of the type of wheal produced by the reverse technique.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Vitamin C and Peptone Shock in Dogs. Dragstedt, C. A., Eyer, S. W., and De Arellano, M. R.: Proc. Soc. Exper. Biol. & Med. **38**: 641, 1938.

The authors, in previous communications, were unable to confirm the protective value of vitamin C against anaphylaxis in the dog. In order to test the protective effect of vitamin C in a histamine-liberating reaction which is not dependent upon

an antigen-antibody reaction, the authors studied the effect of the prior administration of vitamin C upon the severity of peptone shock in dogs.

Eleven dogs, anesthetized with ether and sodium amytal, received injections of cevitamic acid intravenously in amounts varying from 25 to 100 mg. per kg. After varying intervals of from fifteen to forty-five minutes, the animals received an injection of 2 c.c. per kg. of a 10 per cent solution of proteose peptone.

Definite shock occurred in 10 of the 11 animals. The presence of histamine in the blood was demonstrated in all instances in which the reactions were severe.

The authors conclude that the prior injection of vitamin C in dogs does not protect against peptone shock.

Sensitization to Simple Chemicals. Relationship Between Chemical Structures and Properties and the Sensitizing Capacities in the Production of Eczematous Sensitivity in Man. Sulzberger, M. B., and Baer, R. A.: J. Invest. Dermat. **1**: 45, 1938.

The authors report their investigations on the experimental production of contact dermatitis sensitivity in human beings with five different chlor-nitro-substituted benzenes: (A) 1-2-4 dichlornitrobenzene, (B) 1-4-2 dichlornitrobenzene, (C) 1-2-3 chlorodinitrobenzene, (D) 1-2-4 trinitrobenzene, (E) 1-3-5 trinitrobenzene, These were selected from a list of about 20 compounds, whose structural characteristics and chemical properties in vitro, as shown by Landsteiner and Jacobs, closely paralleled their sensitizing capacities in the skin of the guinea pig.

Compounds A, B, and C were used for the experimental sensitization of 15 female subjects. Only compound C elicited the typical picture of human contact dermatitis in the majority of the test persons. This sensitization was demonstrated by the spontaneous flare-up of original test sites after incubation periods of from nine to twelve days and by reactions to patch tests with dilutions after a lapse of from twenty-one to forty-nine days. This result is analogous to that obtained by Landsteiner and Jacobs in guinea pigs. The C compound is alkali labile and combines with organic bases, whereas compounds A and B are alkali resistant.

Compounds D and E were injected intradermally in five subjects at daily intervals for ten days. Compound D produced a papular forty-eight-hour tuberculin type of sensitivity and also a typical contact dermatitis type of sensitivity in all five test persons. In these experiments the D compound acted in producing human contact dermatitis in a manner paralleling the skin-sensitizing properties Landsteiner and Jacobs observed with this substance in the guinea pig and in a manner in keeping with its alkali lability.

The capacity of these substances for producing a contact dermatitis type of hypersensitivity in human beings seems related to the lability of their Cl and NO_2 groups. Although the authors admit that these results do not offer direct proof that these compounds produce contact dermatitis hypersensitiveness by virtue of their capacity to form conjugates with "body-own" substances, they agree that these results are compatible with such a view.

Studies on Anaphylaxis With Insulin. Bernstein, C., Kirsner, J. B., and Turner, W. J.: J. Lab. & Clin. Med. **23**: 938, 1938.

The authors report their experiments on the production of anaphylaxis in the guinea pig with insulin. Both a highly purified commercial preparation of insulin and crystalline insulin were used in this study.

Guinea pigs were sensitized by three subcutaneous injections at four-day intervals of 0.4 c.c. of a mixture of equal parts of normal horse serum and insulin and by 0.2 c.c. of insulin alone. The animals were shocked after intervals of three and six weeks by the intravenous injections of from 0.2 to 0.4 c.c. of insulin.

The writers demonstrate that anaphylactic shock symptoms at three weeks are more pronounced when horse serum-insulin was used for sensitization but that at six weeks this difference is not demonstrable. Crystalline insulin was found to produce slightly more marked anaphylactic symptoms than the commercial preparations.

Precipitin demonstration is reported as inconclusive. Dale studies of the uterine strip were not performed.

A Contribution to the Shwartzman Phenomenon. Albus, G., and Fischer, K.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **92**: 372, 1938.

The writers report their experiments on the use of pollen antigen as the preparatory factor for the production of the Shwartzman phenomenon.

Guinea pigs and rabbits were sensitized with a mixed pollen antigen by introducing 16 mg. of the dry pollen into the peritoneal cavity by operative procedure. The authors report practically 100 per cent sensitization with this technique. The sensitized animals received preparatory doses of 0.3 c.c. mixed pollen antigen and a similar amount of *B. coli* filtrate in different regions of the abdomen. Following the intravenous injection of *B. coli* filtrate, 50 per cent of the animals developed a typical Shwartzman phenomenon at both sites, which were histologically similar. In control (nonsensitized) animals a Shwartzman phenomenon was produced only at the site prepared with the filtrate. The intravenous injection of a mixture of pollen antigen and serum from pollen sensitized animals provoked no reaction in normal animals prepared with *B. coli* filtrate. The provocative intravenous injection of 2 c.c. of pollen antigen into pollen sensitized animals, prepared with *B. coli* filtrate, resulted in a moderate Shwartzman reaction in 25 per cent of the animals, together with varying degrees of shock symptoms.

Diphtheria Immunization With Finely Atomized Formol Toxoid. Bonsfield, G., and King-Brown, W. W.: Lancet **1**: 491, 1938.

Successful attempts to stimulate the production of diphtheria antitoxin by the intranasal instillation of diphtheria toxoid have been reported by C. Jensen and by Bonsfield. Because of some objections raised to the use of this technique in small children, the authors report their studies on a modification of this method.

Five adults were subjected to two exposures, at fourteen days interval, of 50 c.c. of formol toxoid sprayed into a room. Blood was drawn for antitoxin titer determinations before the first exposure and again ten days after the second exposure.

The writers report that all subjects with a blood antitoxin titer of 1/10 unit or more showed an increase up to 10 units after exposure to the formol toxoid spray. Violent headache, puffiness of the face and slight tightness of the chest occurred following exposure, especially in those cases developing high titers.

To obviate the reactions obtained, the authors recommend the use of a more refined antigen. The suggestion is made that this method of immunization be studied in other diseases.

Studies on Immunity in a Type of Human Allergy (Hay Fever): Serologic Response of Non-sensitive Individuals to Pollen Antigens. Cooke, R. A., Loveless, M., and Stull, A.: J. Exper. Med. **66**: 689, 1937.

The authors, in a previous publication, demonstrated a phenomenon, produced in sensitive individuals by the injection of ragweed extract, due to a specific blocking type of immune body. In the present communication the writers report their investigations on the serologic response of nonsensitive individuals to pollen injections.

Two (group I) of five nonatopic individuals received six intradermal injections of 0.2 c.c. of a mixture of equal parts of low ragweed extract and ragweed reaginic serum. The total dosage for each subject was 6600 P.N. units of ragweed and 6.6 c.c. of serum. The other three subjects (group II) received subcutaneous injections of ragweed extract only once or twice a week for eleven to fifty-six weeks. A total dosage of from 211,000 to 1,055,000 P.N. units was administered.

Injections of ragweed pollen extract into normal nonsensitive subjects did not produce sensitization to ragweed. The serums of the subjects in group I failed completely to show any change in neutralization point or in the immediate reaction on passive transfer. Serologic changes, resembling those previously observed to occur in ragweed sensitive patients after treatment, were induced in group II. These changes were demonstrable by an inhibition of the immediate reaction on passive transfer and by interference with the neutralization of sensitive serum by its antigen. These serologic changes were, therefore, independent of the specific reaction characteristic of this type of allergy. The inhibiting factor was shown to be specific and related to the pseudoglobulin fraction of the serum.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Sensitivity to Cow's Milk in Infantile Eczema. Hill, L. W.: J. Pediat. **12**: 725, 1938.

Hill emphasizes the similarity between normal and eczematous infants, as well as certain differences. The differences are of degree rather than type. Schloss has shown that normal infants may give precipitin and positive intradermal tests after ingestion of cow's milk, not associated with symptoms. The eczematous infant is even more likely to have a positive test to milk, and it seems often to be related to the eczema.

Of a series of 153 eczematous infants, 17 per cent gave positive scratch tests. However, 56 per cent of negative reactors were positive when tested intradermally with Lederle whey 1:1,000. This was in contrast with 10 per cent positive intradermal reactions in a group of 50 normals, and with 15 per cent positive reactions to goat's lactalbumin used as a control.

In a small series of 19 eczematous infants whose intracutaneous test was positive, 74 per cent made a striking improvement on the milk-free preparation, Sobee. It is also pointed out that most of the cases also give positive skin reactions to wheat, goose feathers, house dust, or other antigens, including egg.

Allergy in Childhood. I. The Modes of Its Acquisition. Ratner, B.: J. Pediat. **12**: 730, 1938.

The author reviews the experimental background relating to this subject. He emphasizes the points in common between human atopy and anaphylaxis in animals. Examples of antibody in human serum mediating allergic reactions in animals and the reverse are given. The implication is that factors known to induce allergy in animals operate in inducing allergy in man. These involve intrauterine sensitization, ingestion, inhalation, and injection; that is, the crossing of the placental, intestinal, respiratory, or skin barriers by unaltered protein. An inherited susceptibility to sensitization is also mentioned as a factor, and the author states he

is not presenting evidence on that phase of the subject. However, he concludes that quantitative considerations concerning the amount of antigen actually absorbed have more to do with the capacity to become sensitized than have qualitative considerations.

Allergy in Childhood. II. Prophylaxis. Ratner, B.: J. Pediat. 12: 737, 1938.

Since he feels all individuals irrespective of inheritance are "potentially" capable of developing allergy, Ratner believes the subject of prophylaxis should receive greater attention. To prevent intrauterine sensitization he proposes for the pregnant woman to limit the protein intake; to prevent the indulgence of cravings and food debauches; to reduce the total quantity of foods in groups with a common antigen, such as fish and nuts; and to alter proteins, where possible, by heat, as in the case of eggs and milk.

The same precautions should be followed in early childhood and during illness and convalescence, as these are periods of greatest vulnerability and mucous membrane permeability. Specifically, complementary or supplementary bottles should be of denatured milk, too early introduction of new foods in the infant's diet should be discouraged, and overeating of seasonal foods should be avoided.

Dust sensitivity depends usually on exposure to dust, and can be prevented by attention to the nursery.

The belief that infectious processes are commonly aggravated by the allergy induced by previous attacks, is an additional reason for trying to prevent such bacterial allergy from becoming established, particularly in respiratory infection.

It is proposed to reduce horse serum sensitivity by avoiding the inhalation of dander, the act of "hippophagy," and the more considered and judicious use of horse serum, especially in the form of tetanus antitoxin.

Although the individual instances cited all illustrate the absence of constitutional factors as being of significance in the development of allergy, the author surprises one by concluding that "constitutional differences in children make for a greater or lesser vulnerability to the development of allergy."

Relative Value of Diagnostic Procedures in the Allergic Child. Stoesser, A. V., and Cutts, R. E.: Minnesota Med. 21: 418, 1938.

Three hundred consecutive cases of allergy were studied by a routine which included first pressure puncture through concentrated glycerin extracts, then elimination diets, then intracutaneous tests, and finally less specific methods, such as the local treatment of eczema and removal of tonsils and adenoids. The results of treatment based on the multiple pressure puncture skin test were satisfactory in 48 per cent of cases. The best results were in hay fever and asthma, the poorest in allergic rhinitis, urticaria, and gastrointestinal allergy. Excluding nine unsuccessfully treated hay fever cases, there remained 147 children unrelieved, and they were given elimination diets. Twenty-seven per cent responded favorably, and urticaria and gastrointestinal allergy responded best in this group. Asthma was the least relieved by elimination diet. The remaining 108 children were tested intradermally, and 35 per cent made satisfactory responses to treatment based on the results. Allergic rhinitis and asthma made the best showing here. In review, it seemed that in eczema the elimination diets and pressure puncture tests were of greatest help; in allergic rhinitis, the intracutaneous test; in hay fever, the pressure puncture method; in asthma, both forms of skin tests; and in gastrointestinal allergy and urticaria, the elimination diets.

Rhino-Ophthalmology

UNDER THE DIRECTION OF FRENCH HANSEL, M.D., ST. LOUIS

Allergy as Related to Otolaryngology. Swann, C. C.: Arch. Pediat. **53**: 730, 1936.

According to the observations of Swann, from 20 to 30 per cent of sinus disease is of allergic origin, and in cases of chronic disease the incidence of allergy is much greater. Any patient with a history of frequent colds, sneezing, itching of the nasal mucous membrane, nasal discharge, and nasal obstruction, edema and pallor of the mucous membranes should receive a thorough study to determine the possibility of the presence of nasal allergy.

Studies in Asthma: The Nose and Throat in Five Hundred Cases of Asthma. Weille, F. L.: New England J. Med. **215**: 235, 1936.

Weille presents his observations on the condition of the nose and throat in 500 cases of asthma. Almost half of the patients were between the ages of 30 and 50. Sinusitis was present in 362 cases. Among 290 patients who had no drainage of the sinuses, bronchoscopy, removal of polyps or of teeth, tonsillectomy, or other operation, 142 had slight or severe sinusitis, 15 had pansinusitis, 18 had infected, 20 severely infected tonsils, 25 had abscessed teeth that were untreated, and about two-thirds were improved or cured. The rest remained the same or became worse.

Nasal Ionization. Histologic Studies in Relation to Clinical Evaluation. Hollender, A. R., and Fabricant, Noah D.: Arch. Otolaryng. **27**: 452, 1938.

Hollender and Fabricant present a very comprehensive histologic study on the nasal mucosa following nasal ionization. No histologic evidence has been produced to prove that nasal ionization is a harmful therapeutic procedure. They concluded that the evaluation of this procedure should be based solely on clinical observation until more conclusive histologic evidence of the effects of nasal ionization is available.

Inflammatory Bronchial Tumors. Report of a Case and Review of the Literature. Pollak, Berthod S., Cohen, Samuel, and Gnassi, Angelo: Arch. Otolaryng. **27**: 426, 1938.

Pollak, Cohen, and Gnassi present a very comprehensive review of the literature on inflammatory bronchial tumors. The increasing recognition of these lesions is a result of the greater use of the bronchoscope and the increasing knowledge of the mechanical and biological sequelae of these lesions. Since dyspnea is often an outstanding symptom in these cases, they must not be erroneously diagnosed as bronchial asthma.

Treatment of Vasomotor Rhinitis and Allied Conditions With Sodium Morrhuate. Preliminary Report. Fishop, Frank E.: Arch. Otolaryng. **27**: 413, 1938.

For those cases of nasal allergy refractory to the ordinary methods of treatment, Fishop recommends the injection of sodium morrhuate into the inferior turbinates. After cocainization of the mucosa, 0.25 to 0.5 c.c. of 5 per cent solution of sodium morrhuate is injected between the periosteum of the turbinate and the overlying mucosa. Injections may be given at several points in the turbinates at the same time. Small amounts of fluid are injected at each point. The technique and results obtained were illustrated in seven case reports. On the whole, the results obtained were considered most satisfactory.

Miscellaneous

Further Observations on Allergic Disorders of the Urinary Tract. Litzner, S.: Deutsche med. Wchnschr. **63**: 1546, 1937.

Two cases with typical symptoms of renal colic are described in which detailed study revealed no pathologic findings. Each had suggestive findings of allergy, particularly a high eosinophile count in the blood, and, of particular interest, the urinary sediment was rich in eosinophiles. Both patients gave positive skin reactions to foods, and elimination diets based on these findings induced much improvement. For the acute episodes, ephedrine gave more satisfactory relief than other drugs.

Skin Tests for Pregnancy. Lass, P. M., Enderle, E. S., and Kurzrok, R.: Endocrinology **22**: 71, 1938.

The gonadotropic substance used was obtained by alcohol precipitation of the urine of human pregnancy. The precipitate was dried and dissolved in distilled water. One-tenth cubic centimeter was injected intradermally. Typical wheal formation often with pseudopods compared to a control was considered positive. One hundred and eight pregnant patients were tested, of which 8 gave positive and 100 negative responses. Of 25 nonpregnant normal women, 9 gave positive and 16 negative reactions. A third group of 100 nonpregnant women, all of whom were allergic to one or more substances, were injected, and 47 gave positive and 53 negative response. Antigen prepared from human placental tissue, with a control of amniotic fluid, was given to 73 pregnant women. This test was positive 35 times, doubtful 26 times, and negative in 12 women. When given to 15 normal patients, 3 gave a positive reaction; of 20 males, 5 were positive. It is concluded that the test, with the conventional antigens used, is neither reliable nor of any value in clinical medicine.

Physical Allergy. Goodson, W. H.: Proc. Staff Meet., Mayo Clin. **13**: 500, 1938.

The author reviews the recent observations by others on this subject and brings them up to date. He also gives the results of his analysis of the literature and states that in approximately 50 per cent of the cases encountered, a positive family history of so-called allergic disorders was given. In the majority of cases the symptoms began in the second or third decade. In most instances the onset was insidious, but in approximately 25 per cent it seemed to spring from acute febrile illness. The most effective treatment seemed to be systematic repeated exposures to the exciting agent. Injections of small doses of histamine, beginning with 0.05 mg., once or twice daily, and gradually increasing to a dose of maximal tolerance, is often effective. Histaminase seems to offer definite possibilities, but must be further investigated.

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